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SCLEROSING HEMANGIOMAS

THEIR RELATIONSHIP TO DERMATOFIBROMA, HISTIOCYTOMA, XANTHOMA AND TO CERTAIN PIGMENTED LESIONS OF THE SKIN *

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The histologic classification of tumors is often decided by comparing average fields in different lesions and grouping together those which match most closely. Changes of secondary character, however, may make tumors of the same origin appear to be different on superficial examination. As a result, tumors originating from identical cells have come to be known by several different names. If the classification is based on the cells of origin, and the relation of secondary changes to the final tissue pattern is recognized, then one can establish groups of tumors which are similar in origin and behavior.

Few, if any, classes of tumors have become more confused by the practice of matching average pictures than have the hemangiomas. Pathologists and clinicians have long recognized as hemangiomas the red or bluish cutaneous lesions which histologically are composed of capillaries or cavernous blood spaces. They have also observed some blood vessel tumors of the skin to undergo regression or even to disappear without treatment. Regression may be precipitated by local injury, by surface ulceration, or by superimposed infection. These changes are well known; an extensive study of them has been published by Lister.[1]

It is not well known that a process of sclerosis without detectable antecedents frequently occurs in hemangiomas, a process which results in striking changes in the gross and microscopic appearance of these lesions. The overgrowth of fibrous tissue in hemangiomas leads, by a definite series of histologic sequences, to the accumulation of fat and hemosiderin. These changes take place in varying degrees, one predominating in one specimen, another in another. The process of sclerosis may, therefore, lead to a number of different end-results.

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The tumors when removed are often in one or another of these end-stages, the steps in the progressive tissue sequences being obscured. When the lesions are deeply pigmented with hemosiderin, they have been confused clinically and even pathologically with melanomas (Figs. 1 and 10). When they are filled with fat, they are sometimes regarded as cutaneous xanthomas (Figs. 3, 5 and 11) or "giant cell xanthomas," if there are many giant cells in addition to the lipoid-filled cells. When the connective tissue overgrowth is prominent and accumulation of both fat and hemosiderin is slight, the lesions have been placed in the group of unencapsulated fibromas (Fig. 7). The terms *histiocytoma*, *dermatofibroma* and other names have been applied to one or another phase of sclerosing hemangiomas.

It seems, therefore, advisable to trace the process of sclerosis in hemangiomas through a series of the lesions. In this way, the possible variations may be defined more clearly and the essential similarity of lesions which appear very different may be established. The identification of these lesions as sclerosing hemangiomas is important because it shows that they are benign and localized; they are not cutaneous manifestations of a generalized disease. These microscopic changes were recognized and described briefly by one of us (S. B. W.)[2] in 1913; the present material is in accord with the views expressed in that paper.

Material for Study

All records and microscopic sections of hemangiomas from the files of the Departments of Pathology of the Peter Bent Brigham Hospital and the Children's Hospital were reviewed. The great majority of these hemangiomas were from surgical specimens; only a few had been removed at autopsy. Those which showed histologic pictures suitable for inclusion in the category of "sclerosing hemangioma" were selected for study. A total of 67 specimens was thus obtained, and from this material the following descriptions have been made. Paraffin sections in all instances were stained with either eosin and methylene blue, or hematoxylin and eosin. The majority were stained also with phosphotungstic acid hematoxylin and Mallory's aniline blue connective tissue stain. Many were studied with fat stains (scharlach R) applied to frozen sections of formaldehyde-fixed tissue and with iron stains (Berlin blue or Turnbull's blue) on paraffin sections. In some instances Foot's reticulum stain, Weigert's elastic tissue stain, and osmic acid staining for fat were used for demonstration of special features.

Distribution and Gross Appearance of Sclerosing Hemangiomas

The 67 sclerosing hemangiomas from 66 patients were distributed as follows:

Upper extremity		15
Location on extremity not specified	4	
Upper arm	1	
Forearm	3	
Wrist	1	
Palm	1	
Fingers	5	
Lower extremity		29
Location on extremity not specified	4	
Thigh	6	
Around knee	5	
Calf	2	
Shin	6	
Ankle	2	
Foot	2	
Toes	2	
Face		5
Eyelid		2
Shoulder		3
Breast		3
Abdomen		2
Buttocks		3
Back		1
Scattered		1
Region not stated		3

When grouped according to age of the patients, the following results were obtained:

Age in years	Number of patients	Percentage of series
0–9	5	7
10–19	8	12
20–29	9	13
30–39	14	21
40–49	15	23
50–59	7	11
60–69	2	3
Age not stated	6	10

Eighty per cent of the patients were between the ages of 10 and 59 years; 44 per cent were between 30 and 49 years. The high incidence of sclerosing hemangiomas in the older decades is in distinct contrast to the relative frequency with which cutaneous (unchanged) hemangiomata are observed in childhood as compared with adult life. This provides some evidence that the sclerosing process requires years or even decades to be completed.

Cutaneous sclerosing hemangiomas are commonly limited to the skin and subcutaneous fat. It is rare for them to extend as deeply as the superficial fascia or the skeletal musculature. The records indicated considerable variety in the size, shape and color of the skin lesions. The smallest were but a few millimeters in diameter; others were as large as 4 or 5 cm. in cross dimensions (Fig. 1). Average examples were 8 to 12 mm. in diameter. Most of them were flat lesions, covered by skin which was somewhat smoothed out. At times, however, the overlying skin retained its normal dimples and fissures. The lesions usually lay in the corium and subcutaneous fat and did not project above the level of the surrounding epidermis. In only a few examples did they rise appreciably above the adjacent skin; one specimen was pedunculated. The color ranged from a gray or pinkish gray (when fibrosis was extensive) to a pale yellow (when lipoid deposits were heavy) or to tan-brown (when pigment accumulations were marked) (Fig. 1). Frequently the patient would volunteer the information that a "birthmark" or typical angioma had been present for many years but that subsequently it had gradually assumed its present appearance.

Cross sections of some examples showed little more than a thickening and increased stiffness of the corium; generally there was sufficient fibrosis to give the specimen a firm consistency. Usually the lesion could be clearly outlined with the naked eye, but there was no encapsulation and the pathologic tissue merged into surrounding normal structures (Fig. 6). If there was a large amount of fibrosis, the fresh tissue had a light gray or pearly appearance. If large quantities of lipoid were present, the cut surface was yellow, with the intensity directly related to the amount of accumulated fat. Similarly, deposits of pigments imparted varying shades of tan or brown to the cut surface (Fig. 2) depending upon the amount present.

Histologic Sequences in Sclerosing Hemangiomas

In all hemangiomas there are two tissues—the blood vessels and a supporting connective tissue stroma. The process of sclerosis consists of an overgrowth of the stroma; in most instances the increase in connective tissue initiates a series of histologic sequences which might appear to be entirely unrelated.

The extent of connective tissue overgrowth is extremely variable. When a number of specimens are studied all gradations of sclerosis can be identified, from that which is but a slight increase over the usual stroma to that which represents almost complete obliteration of the

blood vessels by dense collagenous tissue (Fig. 8). Occasionally, the fibrosis is so marked that it is almost impossible to recognize the hemangiomatous origin of the lesion. Different areas in a single specimen may also show wide variations in the amount and character of connective tissue proliferation. Often, there is a well advanced sclerosis in the central portion of the specimen while the peripheral zones show actively proliferating angiomatous tissue little affected by the process of sclerosis. The intervascular connective tissue may be very cellular and composed of large, young fibroblasts or it may have a low cellularity and be composed of shrunken, mature, connective tissue cells with a large amount of collagen. In the latter cases, the collagen is often hyalinized.

While collagen may be extensively formed, elastic tissue is rarely found; when elastic fibers are seen, they are short, thin and widely separated, compared to those of normal corium. The fibers appear to be those of the corium present before the process of sclerosis was initiated. The elastic tissue does not seem to be newly formed in the connective tissue overgrowth.

The sclerosing process has a distinct effect on the vascular network in the hemangiomas. Concentrically arranged fibroblasts encircle and constrict individual capillaries. The gradual contraction of connective tissue compresses the blood vessels of the lesions so that their lumina are progressively reduced in size. Portions of the vessels are then cut off from the circulating blood stream, and obliteration of channels finally occurs. The progressive occlusion of the angiomatous channels is seldom accompanied by thrombosis. After complete closure of vessels has taken place, the cords of remaining endothelial cells are broken up and nests of them become pinched off in such manner that their relation to the rest of the blood vessel is lost.

The endothelial cells, thus isolated, at times coalesce to form giant cells (Fig. 9). Giant cells were found in 18 of the 67 specimens in the series. In some of the 18 tumors, the cells were few but occasionally they were so numerous as to dominate the histologic picture. In sclerosing capillary hemangiomas, cords of obliterated vessels give rise to giant cells. In those specimens where a more rapid growth is evident (hemangio-endothelioma), sheets of endothelial cells appear to differentiate directly, either into capillary blood vessels or into giant cells. Wolbach,[2] and later Kirch,[3] described hemangio-endotheliomas of the skin which had become so altered that they possessed the histologic appearances of giant cell xanthomas; the present report is in entire agreement with the views expressed in these two papers.

The giant cells are of the "foreign body" type, and contain from two or three to as many as twenty or more nuclei (Fig. 9). Their cytoplasm takes a deep stain and is more basophilic than that of surrounding cells. It is often homogeneous. In some areas, however, the cytoplasm of the giant cells contains fat droplets, or hemosiderin, or both. These materials often accumulate in other cells of endothelial origin in sclerosing hemangiomas, as subsequently described.

One of the most striking results of the overgrowth of stroma in hemangiomas is the accumulation of hemosiderin (Fig. 4). Of the 67 specimens on which the present study is based, pigment deposits were marked in 7, moderate in 9, slight in 12, and absent in 39. While some of the pigment is free in the tissues, most of it is within the cytoplasm of endothelial cells. The evidence that the cells are of endothelial origin lies in part in their morphologic resemblance to the cells lining nearby blood vessels. Additional evidence is derived from the fact that hemosiderin is occasionally seen in endothelial cells lining still patent capillaries in these lesions (Fig. 10). The amount of pigment in some cases is so great as to impart a deep brown color to the lesions (Fig. 1). These deeply pigmented sclerosing hemangiomas are easily confused clinically with melanomas.

It is difficult to explain the most marked degrees of pigmentation by disintegration of entrapped red blood cells alone, especially in view of the fact that there is no definite correlation between degree of pigmentation and degree of sclerosis. In occasional specimens there is evidence of old or recent hemorrhage, and some of the pigment is possibly derived from this source. In the vast majority of cases, however, no hemorrhage is apparent and the source of the excess pigment remains unexplained.

The pigment is light golden brown, is doubly refractile and has all the appearances and staining reactions of hemosiderin. It is found in globules of irregular shape and size, in contrast to the rather small, rounded, and more uniform size of melanin granules (Smith [4]). It is stained an intense blue by the Berlin blue and the Turnbull's blue reactions (Fig. 4)—a fact which establishes the differentiation from melanin. This test can be made on Zenker-fixed material embedded in paraffin but formaldehyde-fixed material is to be preferred. When it is necessary to make a rapid diagnosis, Turnbull's blue reaction can be done on frozen sections and completed within a few minutes. The sections are immersed for 10 to 15 seconds in a saturated solution of ammonium sulfide. They are then transferred for a similar period into a solution made of equal parts of 1 per cent hydrochloric acid and 20 per cent ammonium ferricyanide. In such sections the blue-staining

material can be easily identified microscopically, or, if the pigment is present in sufficient quantity, there appears a blue color which can be seen grossly.

Fat is often taken up by endothelial cells derived from the segmented, compressed and disrupted vessels (Figs. 3, 5 and 11). In the present series of 67 sclerosing hemangiomas, lipoid accumulations were extensive in 12, moderate in 15, slight in 13 and absent in 27. Fifteen of the 67 specimens showed neither lipoid material nor hemosiderin.

As already suggested in the discussion of hemosiderin accumulation, it appears that the tendency toward phagocytosis on the part of endothelial cells is increased when they become isolated as the result of an increase in the surrounding connective tissue stroma. However, neither the accumulation of pigment nor the appearance of fat is necessarily most marked where the fibrosis is most advanced. Either may be completely absent in one part of a specimen and yet be prominent in nearby microscopic fields. The evidence that the lipoid phagocytes are endothelial in origin is of the same character as that for the endothelial nature of the cells containing pigment—their morphologic similarity to normal endothelial cells and the appearance of fat in cells lining patent capillaries in the lesions (Fig. 11). Further evidence that the phagocytes are identical in origin is afforded by the fact that lipoids and hemosiderin at times appear within the same cell (Fig. 3).

The nature and source of the fat is by no means a settled problem. The lipoid dissolves out in preparations which employ alcohol in the fixation, staining, or mounting of the sections. It stains an intense red when formaldehyde-fixed material is treated with scharlach R. It usually does not stain black in osmic acid preparations, and when it does so, only a small portion of the fat exhibits this reaction. It is seldom that cholesterol crystals (or clefts) can be identified. However, when these do occur, they strongly suggest that some small part of the intracellular, phagocytosed fat is related to or derived from cholesterol or cholesterol esters.

We [2] have regarded the fat in sclerosing hemangiomas as probably being nutritional fat; that is, fat of the same character as that found in the circulating blood under normal conditions. It is difficult to account for the large amount of lipoid material found in some sclerosing hemangiomas on any other basis. Disintegrating red blood cells have a rather high fat content. However, they are not present in amounts sufficient to contribute more than a small part of the lipoids in the examples where the fat is more abundant. It appears certain, however, that the lipoid accumulations of sclerosing hemangiomas are due to tissue reactions within the lesions themselves. Complete autop-

sies on patients with sclerosing hemangiomas have not shown any evidence of a generalized disturbance of lipoid metabolism; there was no clinical evidence of such disorder in patients on whom autopsy was not performed.

The histologic sequences which accompany the process of sclerosis in hemangiomas represent regressive phenomena. Their end-result is a scar consisting chiefly of dense connective tissue. If most of the blood vessels have been obliterated and the fat and pigment have disappeared, it may be impossible to identify the original nature of the lesion. At the stages in which the accumulation of fat and pigment are so striking, the angiomatous origin of the lesions may be overlooked.

Since the sequences involved are essentially regressive, they indicate in general that the hemangiomas which undergo these changes have been present for a long time and are benign lesions. However, similar sequences of tissue behavior occur to a slight degree in portions of more rapidly growing tumors of blood vessel origin. The rate of growth is determined by the behavior of the blood vessel elements, not by the overgrowth of the stroma or the secondary tissue changes which result from it.

Discussion

While no adequate statistics for the incidence of hemangiomas or sclerosing hemangiomas in different age groups are available, there is little doubt that the former are particularly common during childhood while the latter rarely appear before adolescent or adult life. It is evident that a hemangioma must usually exist for a considerable number of years before the regressive changes of sclerosis, lipoid accumulation, or pigment deposition take place to any important degree. Minor degrees of these changes can be encountered in hemangiomas removed from infants and children; in general, however, the well advanced and more typical examples of the condition are apt to be found in older persons. Adequate clinical history and observation will often indicate that a hemangioma which was bright red in early years of life has subsequently faded, or has assumed a yellow or brownish color at a later time.

Sclerosing hemangiomas appear on divers parts of the body surface, but the majority (two-thirds) of them are found on the extremities. Since hemangiomas in childhood are more common on the head and neck, whereas the sclerosing hemangioma of later life is more apt to be found elsewhere on the body, it is suggested that the sclerosing processes are more prone to arise in those hemangiomas which are subjected to minor trauma. Indeed, it is conceivable that the mild but

repeated and chronic irritation of clothing on a soft and delicate structure such as a hemangioma can incite the fibrosis and other retrogressive features which have been described.

Sclerosis is not necessarily limited to those hemangiomas which are situated on the surface of the body, but it appears with greater frequency in hemangiomas of the skin. Fibrosis and lipoid accumulation in these tumors have been observed in various internal viscera, particularly those of the liver. Cushing and Percival Bailey [5] have noted similar changes in angiomas of the cerebellum; in some cases fat and pigment deposits were so extensive that the gross specimens had a vivid yellow or orange color. Orville Bailey and Ford [6] have recorded observations on sclerosis in hemangiomas of the central nervous system—a process which is believed to be similar to the pathologic sequences here recorded for the sclerosing angiomas of the skin. In short, the secondary changes of fibrosis (or gliosis) and the accumulation of fat or pigment appear to be inherent potentialities of hemangiomas anywhere in the body.

The preoperative (or ante-mortem) diagnoses in these cases were seldom correct. The grayish color (or in some cases a lack of discoloration of the skin) combined with a firm, intracutaneous or subcutaneous mass, frequently led to diagnoses of fibroma or neurofibroma. Occasionally these lesions were thought to be sebaceous cysts. The tan or brownish variety were almost always diagnosed as pigmented nevi or melanomas. It is doubtful if any high degree of accuracy can be attained in preoperative recognition of these lesions unless there happens to be a history which suggests that they formerly had a definitely angiomatous character.

It should be emphasized again that the accumulation of hemosiderin and lipoid materials are strictly localized processes and are not a part of a generalized metabolic disturbance. Sclerosing hemangiomas must therefore be differentiated from the cutaneous changes (*xanthoma cutis diabeticorum*) found in diabetes mellitus with lipemia. In this latter condition the cutaneous pathology is presumably the result of tissue reaction to extravascular deposits of lipoids. Sclerosing hemangiomas containing large accumulations of fat must also be set apart from *xanthoma planum, xanthoma tuberosum* and *xanthoma disseminatum*. These metabolic disturbances have been admirably discussed by Thannhauser and Magendantz [7] and others; it is not necessary to redescribe them here, but it is important to emphasize that they are totally unrelated to sclerosing hemangiomas.

We do not wish to suggest that all xanthomas of the skin which are not a part of a systemic disease are necessarily derived from heman-

giomas. There are other localized forms of cutaneous tumors containing large amounts of fat within phagocytic cells.

In the present series of specimens there were some with giant cells which were apparently derived from endothelial cells of the angioma (Fig. 9). The finding of such giant cell xanthomas of the skin—which obviously had their origin in hemangiomas—raises the possibility that some giant cell tumors in other parts of the body may be similarly derived from hemangiomas. It is suggested that giant cell tumors of tendon sheaths develop in such a manner. Bellamy [8] has also supported such a view; he listed as important characteristics of giant cell tumors of tendon sheaths "the presence of adult connective tissue, certain proliferating cells, multinucleated or giant cells, blood vessels with actively proliferating endothelium, and finally advanced stages of fatty degeneration." From his studies he concluded that these do not belong among the "giant cell tumors" but that, owing to the fact that their evolution is due to proliferation of the endothelial cells of the blood vessels, they should be called endotheliomas. Garrett [9] also concurred with this opinion. It is probable that such secondary changes in hemangiomas account for the formation of some, if not all, of the giant cell tumors of joints, which are almost entirely limited to the lower extremity and which are most frequently found in the knee. A high vascularity, accumulations of lipoids and pigment, and formation of giant cells are common findings in these neoplasms which arise from the synovia and which project into the joint cavity or extensively involve the joint capsule. Many authors, among them DeSanto and Wilson,[10] are convinced that the giant cells are derived from the reticulo-endothelial system. It is not pertinent to the present communication to pursue this thesis further except to suggest that some "xanthomas" or "giant cell xanthomas" of the tendon sheaths or synovial membranes probably originate from hemangiomas which have been so altered that they are scarcely recognizable as such when the lesions are removed at operation or autopsy, unless the sclerosing process as described here is taken into consideration.

Summary

Certain hemangiomas exhibit spontaneous, regressive changes which greatly alter their macroscopic and microscopic appearances. The initial step is usually dependent upon fibrosis which constricts capillary blood vessels, isolates segments of collapsed channels, and segregates groups of remaining endothelial cells. In about three-quarters of the instances, there are accumulations of lipoid material or hemosiderin, or both. In occasional specimens these substances appear to

come from hemorrhages within the angioma, but this is not true in the majority of cases. The lipoid and pigment are presumably from, and extracted from, substances in the circulating blood. About one-quarter of the lesions show aggregations of endothelial cells forming foreign body giant cells. It is not surprising to find the type-cell of hemangiomas performing the dual rôle of blood vessel formation and phagocytosis since these activities of endothelial cells are well recognized in the normal reticulo-endothelial system of the body.

There is great variation in the prominence of fibrosis, vascular obliteration and phagocytic activity in sclerosing hemangiomas. When connective tissue proliferation is advanced, the lesion is quite firm, grayish, and has the gross appearance of a fibroma or neurofibroma; microscopically, the original angiomatous nature of the specimen may be largely obscured. When phagocytosis of lipoid is an outstanding feature, the gross specimen may have a yellowish color and the microscopic findings may be quite similar to some of the cutaneous xanthomas, but the condition has no relationship to the generalized lipoid disturbances (*diabetes mellitus, xanthoma disseminatum, xanthoma planum,* or *xanthoma tuberosum*). When pigment accumulates in high concentration, the gross lesion has a brownish color and may be mistaken for a melanoma, but the microscopic appearance of the pigment and the positive reaction to iron stains differentiate it from melanin.

The sclerosing process and the phagocytic properties may be exhibited by cavernous hemangiomas and rarely by hemangio-endotheliomas, but they are much more common in the capillary form of hemangiomas. They may be found in hemangiomas in many of the internal viscera, but they appear to be more frequent in those which are situated on the cutaneous surfaces of the body, particularly those which are located on the trunk or the extremities.

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DESCRIPTION OF PLATES

PLATE 59

FIG. 1. Dark brown, flat, cutaneous lesion (life-sized) from a leg of a woman, 32 years old. It overlay the head of the fibula and had been present for many years.

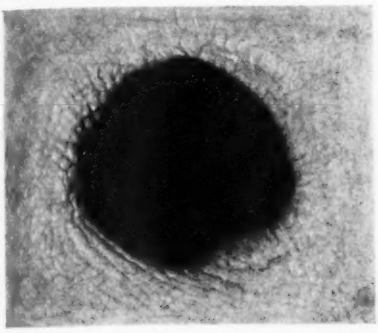
FIG. 2. Cross section of surgically excised specimen shown in Figure 1. Between the epidermis and the underlying subcutaneous fat is a nonencapsulated but rather well circumscribed golden brown tissue which has been formed by the deposition of lipoids and hemosiderin in a hemangioma.

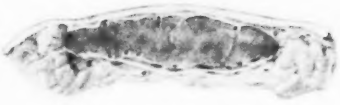
FIG. 3. Same specimen as shown in Figures 1 and 2. Camera lucida drawing from a section stained with phosphotungstic acid hematoxylin. Angioma, showing two vessels of capillary size at the right and a larger one on the left. Connective tissue takes the orange stain. A large portion of the lesion is composed of phagocytic cells filled with lipoids and lesser amounts of hemosiderin.

FIG. 4. Same specimen as shown in Figure 3. Turnbull's blue reaction. All of the pigment stains blue, showing that it contains iron.

FIG. 5. Same specimen as shown in Figures 3 and 4. Frozen section from formaldehyde-fixed material, stained with scharlach R and counterstained with methylene blue. The phagocytosed lipoids take an intense red stain.

1





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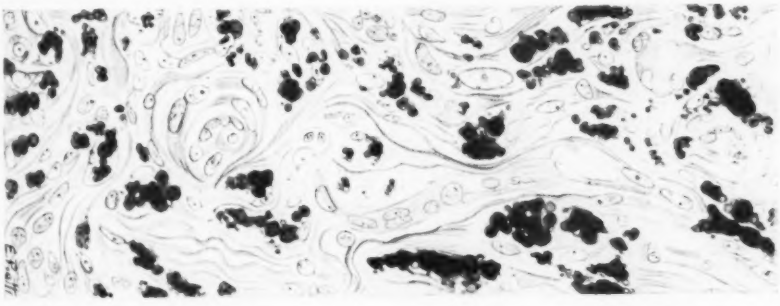

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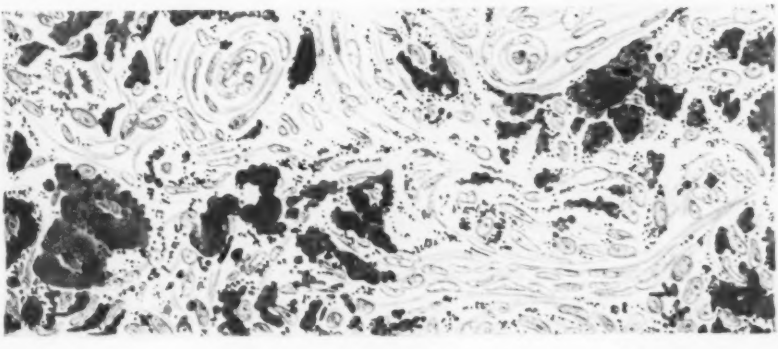
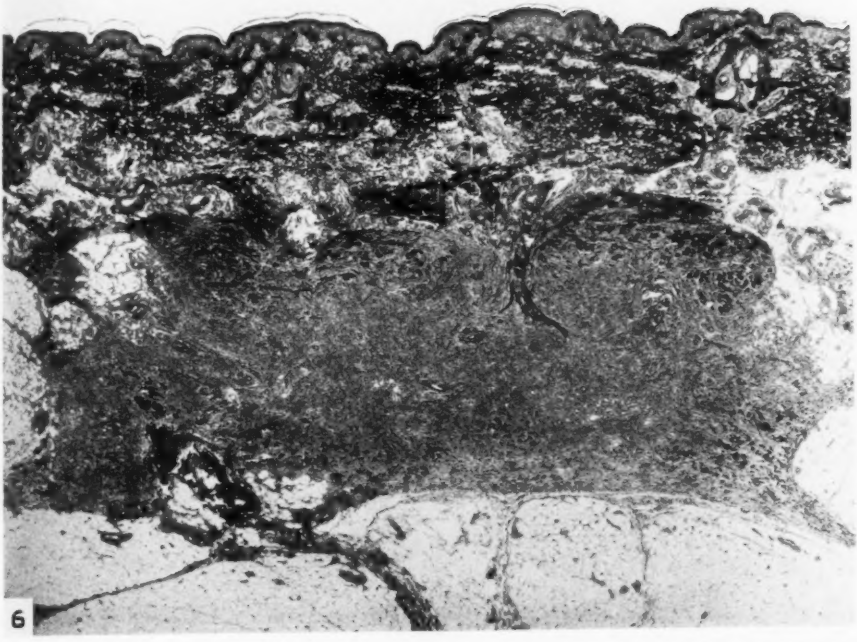


PLATE 60

FIG. 6. Sclerosing hemangioma of the lower leg of a woman, 32 years old. The lesion in the subcutaneous fat is unencapsulated. Such sclerosing hemangiomas as this are confused with unencapsulated fibromas. Eosin and methylene blue stain. × 17.

FIG. 7. Sclerosing hemangioma. There is marked overgrowth of the connective tissue stroma. The capillary indicates the persistence of blood vessel elements in spite of the extent of the sclerosis. There is no pigment or lipoid in this field. Eosin and methylene blue stain. × 590.



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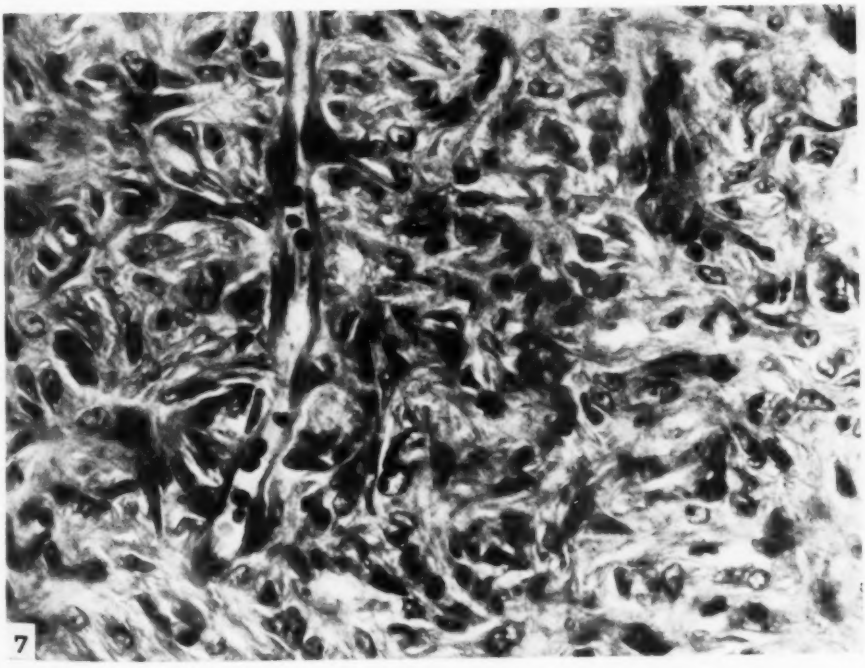


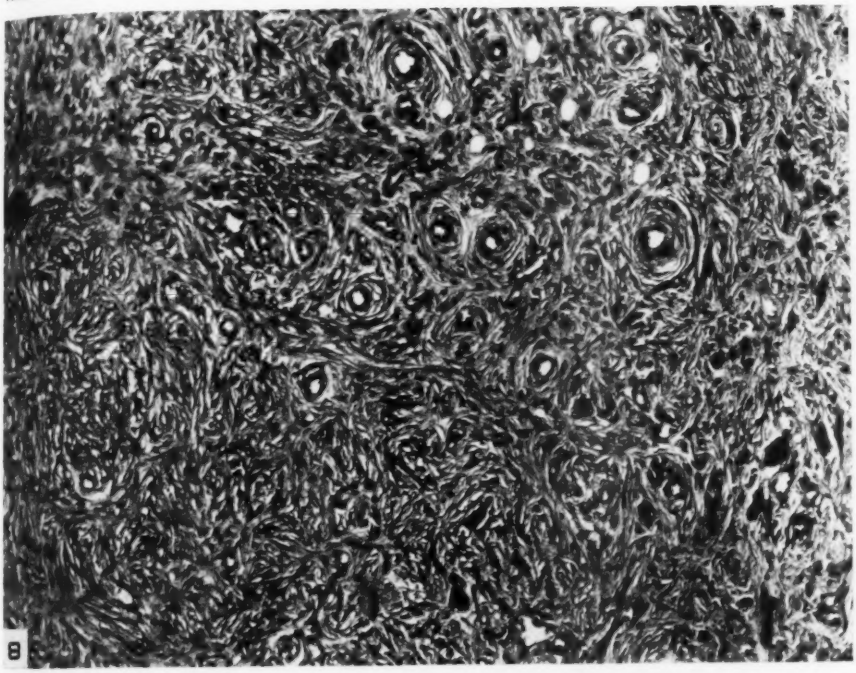
7

Gross and Wolbach Sclerosing Hemangiomas

PLATE 61

FIG. 8. Sclerosing hemangioma of the lower leg. Capillary blood vessels are surrounded by a large amount of connective tissue stroma. Eosin and methylene blue stain. × 125.

FIG. 9. Sclerosing hemangioma of the skin of the buttock. There are numerous multinucleated giant cells. Eosin and methylene blue stain. × 900.



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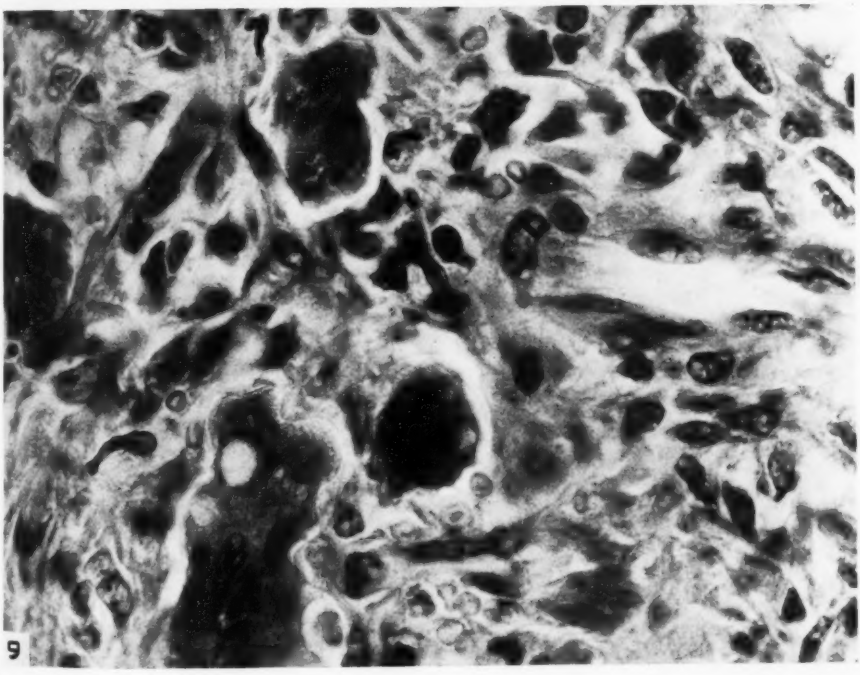


9

Gross and Wolbach Sclerosing Hemangiomas

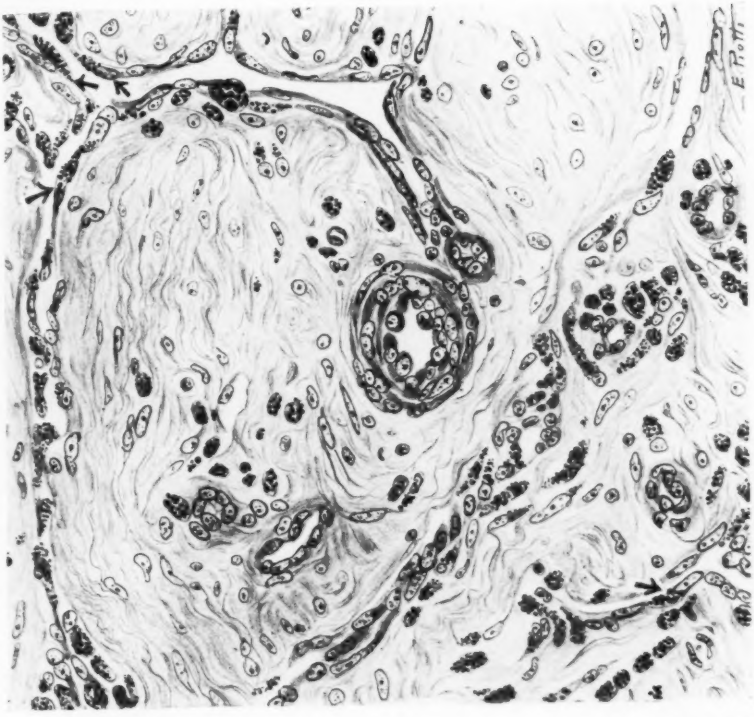
Plate 62

The specimen drawn in Figures 10 and 11 came from a cutaneous lesion of the leg of a man, 39 years old. This lesion was brownish in color and had been noticed for many years.

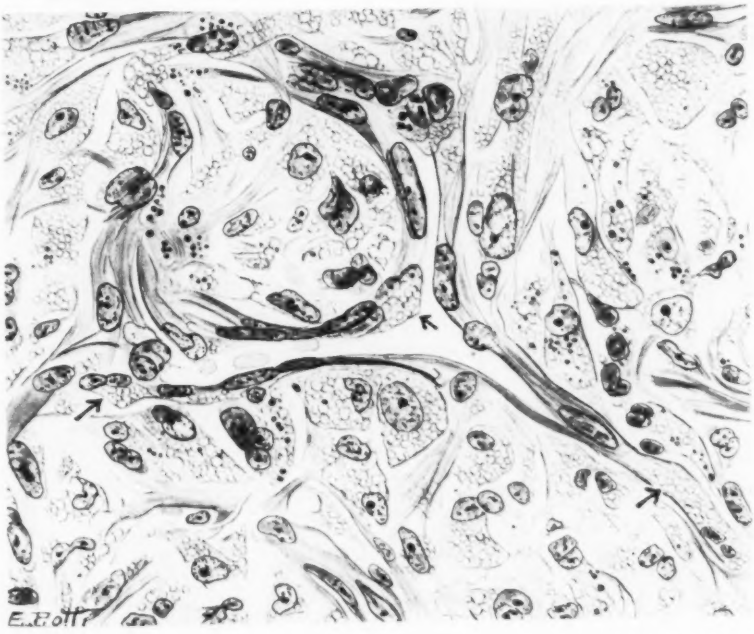
Fig. 10. Camera lucida drawing from a section stained with hematoxylin and eosin. The angiomatous nature of the lesion is shown by the formation of multiple vessels of capillary size. There is an abundant connective tissue stroma, which in some places compresses blood vessels and frequently pinches off and isolates endothelial cells. Phagocytic activity of endothelial cells is exhibited whether they are segregated or are still a part of vessel walls (arrows). The phagocytosed pigment, which is here shown in black, was a light brown in the microscopic sections.

Fig. 11. Same section and stain as shown in Figure 10, showing an area in which myriads of phagocytic cells have taken up lipoids. Phagocytic activity is also shown by endothelial cells (arrows) which are still a part of the vascular channels shown in the center of the drawing.

10



11



CHONDROSARCOMA OF BONE *

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For a while, at least in this country, there was a tendency not to single out chondrosarcoma from the general category of osteogenic sarcoma. One of the first to re-stress the need for this distinction was Phemister,[1] who did so in 1930. Now, the Committee of the Registry of Bone Sarcoma [2] of the American College of Surgeons, in its revised classification, has likewise accepted the concept of chondrosarcoma as an entity among the malignant tumors of bone and specifically as a lesion distinct from osteogenic sarcoma as such. This differentiation has a firm anatomic basis and is important both clinically and prognostically.

Apart from the fundamental anatomic differences between the two lesions, chondrosarcoma is by far the less common. Also, on the average, it appears at a much later age, except in comparison with osteogenic sarcoma complicating Paget's disease of bone. Furthermore, chondrosarcoma ordinarily runs a much slower course than osteogenic sarcoma, not metastasizing to the lungs for years, while osteogenic sarcoma has often already so metastasized at the time of the initial intervention (even though the roentgenographs taken at that time may still appear negative).

The basic anatomic difference between the two lesions is that chondrosarcoma develops out of full-fledged cartilage, while osteogenic sarcoma issues from more primitive tissue, developing out of bone-forming mesenchyme. Ordinarily, in an osteogenic sarcoma, most of the proliferating connective tissue, which may be quite anaplastic, becomes converted into neoplastic osteoid tissue and bone directly, though it usually also forms some cartilage, which in turn tends to undergo rapid calcification and ossification. In an occasional osteogenic sarcoma, osteogenesis may even proceed predominantly via the cartilage stage, and cartilage may thus be a prominent feature in the histologic composition of the lesion. However, even in such an osteogenic sarcoma, if one does not limit the examination to a small field of the tumor, and particularly to the periphery of it, one will also see that in other places the basic proliferating connective tissue is merging directly into neoplastic osteoid tissue and bone. On the other hand, in a chondrosarcoma, though large areas of the hyaline matrix may have become myxomatous or even calcified and ossified, the basic

* Received for publication, October 31, 1942.

proliferating tissue of the tumor is full-fledged cartilage. In contrast to osteogenic sarcoma properly so-called, chondrosarcoma never shows neoplastic osteoid tissue and bone evolving directly from a sarcomatous stroma. These general and anatomic differences, in our opinion, constitute an adequate foundation for distinction between osteogenic sarcoma and chondrosarcoma of bone.

The understanding of chondrosarcoma is still being hindered by the idea that to make a diagnosis of chondrosarcoma on a histologic basis alone is often difficult if not impossible. Individual articles [3-5] and standard textbooks [6, 7] frequently express this idea and use it to explain discrepancies between the gravity of a given case clinically and the lack of clear-cut malignity anatomically and especially cytologically. It is true that the histologic picture does not have to be crudely and obviously sarcomatous to indicate chondrosarcoma. However (as it is one of the main purposes of the present article to show), subtle but tell-tale histologic indications of malignity are already present even in the early stage of the evolution of a chondrosarcoma. They may have to be searched for, particularly in an early lesion, but in any case they can be recognized if adequate material is examined and proper significance attached to relatively inconspicuous cytologic abnormalities.

Oddly enough, the literature reveals hardly any studies which adequately indicate distinctions or transition stages between benign and malignant cartilage tumors of bone on a histologic basis alone. Those articles which deal with the detailed histology of cartilage growths (see, for instance, Spuler,[8] Ernst [9] and Merkel [10]) are almost all old ones. In these, one finds attention concentrated not upon the cellular detail, but upon the intercellular matrix, and in particular upon its fibrillar structure and mucoid transformation. Actually, the findings regarding the cells, and not those regarding the intercellular matrix, are those which are significant in the evaluation of a cartilage growth.

Keiller,[11] in 1925, pointed out clearly the importance of attention to details regarding the cells (and particularly the cell nuclei) as a means of distinguishing between benign and malignant cartilage growths. Our own experience has taught us that a cartilage tumor is no longer to be regarded as benign if, when viable noncalcifying areas are examined, it shows, even in scattered fields: (1) many cells with plump nuclei; (2) more than an occasional cell with two such nuclei; and especially (3) giant cartilage cells with large single or multiple nuclei or with clumps of chromatin. The importance of making the correct diagnosis early resides in the relative amenability of chondrosarcomas in accessible sites to early radical surgical treatment.

In regard to many chondrosarcomas, it is possible, from the clinical course and the roentgenographic and pathologic findings, to show or deduce that they have arisen in lesions originally benign. Thus a chondrosarcoma not uncommonly issues from a solitary benign enchondroma (benign central chondroma), especially of a long tubular bone. Again, a chondrosarcoma occasionally develops out of the cartilaginous cap of a solitary osteocartilaginous exostosis (so-called osteochondroma), perhaps more commonly of a flat bone or a vertebra than of a long bone. Analogously, a chondrosarcoma may grow from one of the numerous lesions in skeletal enchondromatosis or in multiple osteocartilaginous exostoses. A chondrosarcoma which begins its development within the interior of a bone may be denoted as a *central chondrosarcoma,* and one which begins in the cartilaginous cap of an osteochondroma as a *peripheral chondrosarcoma.*

The foundation of our discussion is 15 cases recorded in our files. Of these, 10 were central and 5 peripheral chondrosarcomas. Also, a background for this study has been obtained by reviewing the cytology of the benign growths from which chondrosarcoma so often evolves. Drawing on our files, we studied 27 cases of solitary benign enchondroma and 50 cases (the last 50 of 135) of solitary osteochondroma or osteocartilaginous exostosis.

Gross Pathology of Central Chondrosarcoma

Of the 10 cases of central chondrosarcoma, there were 5 in which development out of a less serious cartilaginous lesion could still be clearly deduced and 5 in which it could not. In the former group there was one example involving the upper end of a humerus (in a girl, 19 years of age) in which the diagnosis of chondrosarcoma was based solely on the microscopic findings, the gross findings hardly giving any cue in this direction. Curettings taken for biopsy were studied originally and a resected specimen 10 months later (Figs. 1, 2, 19 and 20). The resection had been done because the lesion had been growing steadily since taking the specimen for biopsy. If it had not been for the microscopic findings in certain areas of the peripheral cartilaginous cuff of the resected specimen, we might still have regarded this lesion as a benign calcifying and ossifying enchondroma, as we did on the basis of the biopsy material. The patient has shown no recurrence during the subsequent 4½ years.*

*Our experience now includes another case in which a calcifying and ossifying enchondroma at the upper end of a humerus underwent malignant transformation. The patient was a man, 52 years of age on admission, and our original material in this case was merely some curettings for biopsy. On this basis, the lesion was at first regarded as a benign enchondroma, though subsequently we realized that we had "underdiagnosed" it. That this

There were also 2 cases of femoral chondrosarcoma presenting localized spontaneous cortical perforations as an ominous gross feature in lesions which likewise might otherwise have been regarded grossly as benign calcifying and ossifying central cartilage growths. In 1 of these, the original material was an amputation specimen from a man, 59 years of age. In the other, the material was an entire femur, obtained at autopsy from a woman of 79 years who, though she had had difficulty relating to the femur for about 4 years before death, had died from bronchopneumonia and pleurisy. (The material in this case belongs to the Erdheim collection now housed in our laboratory, and the case had previously been reported in full by Makrycostas.[12])

In the case of the man, the amputation had been done at the junction of the middle and upper thirds of the thigh, well above the level of perforation. On cutting through the femur, the surgeon unexpectedly found the marrow cavity of the stump filled with cartilage, and, on curetting upward for several inches, also found cartilage extending above the amputation level (Figs. 3, 4 and 23). However, since permission had been given for amputation and not for disarticulation, nothing further was done at that time. Within 3 months after the amputation, a revision of the stump was done because of local recurrence, and 7 months later a disarticulation was performed because there were now large masses of tumor around the remaining portion of the femur. When the latter was dissected free, it was found to be largely enveloped by semifluctuant tumor masses of various sizes, some of which were covered merely by periosteum while others also had muscle adherent to them. Coronal section of the specimen revealed that except at the end of the stump the medullary cavity was filled with soft, whitish, and obviously cellular neoplastic tissue, extending up into the spongiosa of the metaphysis and part of the neck. Furthermore, one could see that the cortex of the shaft was permeated everywhere by tumor and that there were large pockets, bordered by modified and eroded cortex and distended periosteum and filled with soft, semifluid, or gelatinous neoplastic cartilage. From the gross appearance there could not be the slightest doubt that one was dealing with a chondrosarcoma. (For the microscopic picture at that time, see

was so was borne out by the fact that within 12 months the lesion had become flagrantly malignant even clinically. The upper end of the humerus was now resected and showed a chondrosarcoma which had erupted from the bone in one region. Especially where this was the case, the neoplastic tissue was no longer cartilaginous but rather of a fibrous nature and gray-white in color. It appeared histologically as a rather anaplastic, collagen-forming, spindle-celled sarcoma but showed no ossification. From such areas alone, it would be difficult to surmise that the tumor had developed from an enchondroma. Elsewhere, even in the original calcified and ossified cartilaginous portion of the tumor, there was evidence of activated growth of the dormant cartilage cells.

Figure 24). At present, about 2 years after disarticulation, the patient shows another recurrence, with bulky tumor masses in the groin and also in the pelvis.

There were 2 cases in which the chondrosarcoma was engrafted upon lesions of Ollier's disease (skeletal enchondromatosis). In 1—that of a woman of 56 years—the left lower limb had been bumpy, stubby, and shortened from birth, and its bones (especially the femur and tibia) were filled with cartilage plugs and nodules of widely varying size. Some time before this limb was disarticulated, a perforation had occurred through the cortex of the lower end of the femur medially, and a large cartilaginous tumor mass of gray gelatinous tissue, continuous with the interior of the bone, had developed in the soft parts of the lower half of the thigh, particularly in front. It was in this area that the chondromatous tissue had undergone transformation into a chondrosarcoma, while, in contrast, the cartilage filling the upper half of the femur and all of the tibia showed nothing suggestive of malignant change.

The other case was that of a boy, 19 years of age, whose enchondromatosis seemed to be limited to the bones of the right hand and forearm. In this case, the distal end of the ulna was found distorted by a protuberance measuring approximately 6 by 5 by 5 cm., and the affected area was resected. Both longitudinal and transverse sectioning of the specimen showed that the distortion had been created by a mass of cartilage which was continuous with cartilage in the interior of the ulna, the cortex being defective over most of the region where the mass was situated (Figs. 5 and 6).

We turn now to the 5 cases of central chondrosarcoma in which, at the time of initial examination, the pathologic material yielded no evidence that the sarcoma had evolved out of a less serious central cartilaginous lesion. In these cases, the cartilage growth may have been malignant from its inception. In one instance, that of a man of 39 years, an amputation specimen, presenting a lesion (Figs. 8, 9, 10 and 18) in the lower end of a femur, showed a flask-shaped distention of the affected region, 10 cm. wide, 12 cm. deep and 15 cm. long. The amputation level definitely cleared the tumor so far as the interior of the bone was concerned, but apparently did not clear it in relation to the soft parts and periosteum. Within 6 months after the operation, the femoral stump showed extensive rarefaction and cortical destruction, extending upward for about 10 cm., and there were also evidences of recurrence of the tumor in the soft parts about the stump. Disarticulation was now done. On dissecting the muscles and soft tissues about the femur, whitish, glistening tumor was found to be extending

into the muscles and fat. A sagittal section of the stump showed neoplastic tissue extending 7 cm. up the medullary cavity and directly continuous, through defects in the cortex, with that in the surrounding muscles and fat. About 4 cm. above the main tumor mass, another nodule of tumor, 3 cm. in its longest diameter, was found in the marrow cavity of the stump, the intervening part of the cavity apparently being uninvolved.

We have 1 case of chondrosarcoma developing apparently *de novo* in a short tubular bone, specifically, the basal phalanx of a finger (a rare location). The lesion was as large as a child's fist and the skin was movable over it. The tumor had destroyed most of the phalanx, sparing only the basal part. Indeed, even this part showed ingrowth of a few neoplastic nodules. The tumor tissue was typically lobulated, had zones of cystic softening and hemorrhage, and was sharply delimited.

A somewhat different gross picture (Figs. 7 and 17) was presented by a chondrosarcoma in the lower end of a femur of a man, 29 years old. Though the spongiosa in the affected area was filled with tumor, the general contour of the bone itself in that area was not much modified. However, the whole lower third of the thigh was tremendously enlarged, since the tumor had erupted through the cortex and had grown exuberantly in the soft tissues about the lower end of the femur. The site of eruption of the tumor into the surrounding soft tissues was the thin cortex just above the condyles. This gross picture (early penetration of the cortex of the affected area and lush growth of the tumor in the overlying soft tissues, without much distention of the affected bony part) is nearly always seen in chondrosarcomas starting within a flat bone. Our records include 2 such cases, in both of which the lesion originated in an innominate bone.

In 1 of these cases—that of a man of 31 years—the tumor, starting in the left pubic bone, presented on the outside of the pelvis as a large, lobulated, cystic cartilage mass extending along the inner side of the thigh to the perineum. On the inside of the pelvis the cartilaginous mass produced a tumor which, by rectal palpation, could be found extending to the prostate. The gross material from this case consisted of numerous small, irregular fragments of cartilage, most of which were firm and of a homogenous, glassy, blue-white appearance, though a few were softer and more yellowish, apparently in consequence of degenerative changes. None of the cartilage showed areas of calcareous impregnation and ossification such as one would find if he were dealing with a peripheral chondrosarcoma developing from the cartilaginous cap of an osteochondroma.

In the other case—that of a man of 40 years—the tumor seemed to have arisen in the left acetabulum, had broken into the hip joint, involved the homolateral head of the femur, ischium, and pubic bone, and also formed an elastic tumor mass which spread in the pelvis toward the prostate and overlay its left lobe. Complete removal of the tumor was obviously impossible, but many bits of hyaline and myxomatous cartilage were removed for examination. The patient died about 5 months later at another hospital, and, at autopsy,* a large local tumor mass was found, as well as tumor nodules along the aorta and in the right adrenal, pleura, lungs and heart.

In general, chondrosarcomas of the pelvic region may attain truly fantastic size. This is favored by the difficulties of their radical treatment in this region, the high resistance of chondrosarcomas to irradiation therapy, and the likelihood of delay in the appearance of distant or strategic extensions or metastases. Indeed, an innominate bone which is the site of such a chondrosarcoma not infrequently comes to be embedded, over a considerable area, in a mass of neoplastic tissue 12 inches or more in diameter. In addition to breaking into the hip joint and involving the upper end of the femur, it may even come to involve heavily the sacrum and lumbar vertebrae.

Gross Pathology of Peripheral Chondrosarcoma

As noted, "peripheral chondrosarcoma" is here being used to mean only a chondrosarcoma which starts its development in the periphery (as contrasted with the interior) of a bone, and specifically in the cartilaginous cap of an osteochondroma. Of the 5 pertinent cases on which we have anatomic material and clinical data, 4 apparently were instances of solitary osteochondroma with transformation into chondrosarcoma, while the other was an instance of multiple osteochondroma (multiple osteocartilaginous exostosis) in which one of the outgrowths had undergone malignant change. To judge from our experience (and also from the literature), a solitary osteochondroma seems to undergo malignant degeneration only rather rarely, relatively speaking, when one considers the frequency of solitary osteochondroma among the tumorous bone disorders. The incidence of malignant degeneration of one or more of the osteochondromatous outgrowths in cases (themselves more rare) of multiple osteocartilaginous exostosis seems to be higher, on a case-to-case basis. This impression likewise

* We are indebted to Dr. Samuel H. Rosen of the Laboratory of Pathology, Montefiore Hospital, New York City, for the opportunity of examining the protocol and studying slides from the autopsy material in this case.

appears to be borne out by the literature, which reveals a considerable number of such cases.*

In 1 of our cases (that of a woman of 44 years), the chondrosarcoma developed out of a solitary osteochondroma of the left fourth rib, in which a slowly enlarging tumor mass had been known to be present for 12 years. In the extirpated piece of rib the sternal end was found encased, particularly anteriorly, in a mass of lobulated tissue (Figs. 11, 12 and 21). This tumor mass measured 4 by 3.5 by 2.5 cm. and was covered by a fibrous capsule. It felt firm and elastic in some places and osseous in others. When the patient was seen 3 years later, there was a recurrence at the site of the original operative intervention, the tumor mass now being about three times the size of the original lesion. A wide resection was done, and the neoplastic tissue of the recurrent growth was found composed of large facets of cartilage still showing some evidences of calcification and ossification, especially centrally. On microscopic examination, it also showed (Fig. 22) progression of its malignity cytologically beyond what was apparent in the original specimen. Five years after resection of the recurrent lesion, Mayer [13] reported that there had been no further recurrence in this case.

In a case of costal chondrosarcoma developing in association with multiple exostoses, it was the left sixth rib that was affected, with an almost grapefruit-sized tumor in the midaxillary line (Fig. 13). Exploration showed that the mass overhung and separated the adjacent fifth and seventh ribs. It was also found that anteriorly a few small chondromatous nodules had penetrated the capsule and were separate from the main mass, and that posteriorly the tumor had penetrated the pleura. The mass was resected (though not in one piece), and its gross appearance was again found typical of peripheral chondrosarcoma. Specifically, the interior of the tumor showed a rather heavy sprinkling of bone and foci of calcification among islands of cartilage. Externally, there was an irregular zone of cartilage several centimeters thick in some places and clearly delimited here and there from the interior of the tumor by a line of endochondral ossification.

Within 4 months, this patient showed a local recurrence, and a wider local resection of the chest wall was done at another institution. At

* Since this article was submitted, we have studied systematically our cases of hereditary multiple exostosis. We found that, of the 28 relevant cases, 3 (including the one just mentioned above) had come to show malignant transformation of one or another of the exostoses. However, even this incidence of nearly 11 per cent probably does not represent the true incidence of this complication in this series of cases. All 3 subjects were adults when the malignant growth began to be manifest. Since the great majority of the other patients in our own series of multiple exostosis cases were still children or adolescents, one must allow for the possibility that later in life some of these, too, might develop chondrosarcomas.

this operation the tumorous cartilage was found to be practically without the calcification or ossification so typical of peripheral chondrosarcoma, at least in the original specimen. Several months later there was again evidence of recurrence. The patient died almost 2 years after the original operative intervention, and 4 years after he had first noted the presence of the tumor. At autopsy,* considerable gelatinous cartilage was found beneath the soft tissues of the chest wall. Adherent to the pleura, there was a mass of the same type of tissue, practically filling the entire pleural cavity on the affected side and encasing and collapsing the lung (Fig. 25). There were no visceral metastases. The autopsy confirmed the presence of numerous cartilaginous exostoses on various bones, thus establishing the diagnosis of multiple exostoses already made earlier on a roentgenographic basis.

The case—that of a man of 46 years—in which the chondrosarcoma developed from an osteochondroma on a tibia is interesting in that the patient had been aware for 24 years of a hard lump at the upper and outer margin of this bone. During this time the lesion had grown only very slowly, but, about 2 months before the patient's admission to the hospital, it took on a spurt of growth, apparently after local trauma, and became increasingly painful. On admission a large, hard, bony mass, 6 inches in diameter, was palpable on the anterolateral margin of the tibia 1 inch below the tubercle; and on the anteromedial border, about 3 inches below the joint, a smaller mass was palpable (Fig. 14). At operation it was found that the tumor, which had arisen from the tibia, lay both anteriorly and posteriorly to the interosseous membrane. The neoplastic tissue was removed piecemeal, but not all of it could be removed. Nevertheless, a quart (0.95 liter) of material was obtained and submitted for pathologic examination. Grossly, by piecing the bits together, one could see, as for the tumors of ribs just described, that centrally in the tumor mass there was much calcification and ossification and that peripherally there was an undulating, wide cap of cartilage containing streaks of calcification. About 5 weeks later, the limb was amputated above the knee joint, and during the ensuing 2 years the patient has been free from any evidence of recurrence.

The findings in our other 2 cases of peripheral chondrosarcoma are essentially in line with those already indicated. One was a case of tumor of the left innominate bone occurring in a woman of 30 years who dated her difficulties from a fall 8 years before admission to the hospital. On admission, a huge tumor was palpable on the iliac portion

*We are indebted to Dr. Milton Helpern of the Medical Examiner's Office of New York City for permission to view the autopsy and obtain details of the pathologic alterations in this case.

of this bone. The other case was that of a woman, 59 years of age, in whom the lesion was in the left scapula. Although the scapula had been converted into a lobulated mass of the size and shape of a small football, it was because of neurologic symptoms referable to pressure on the brachial plexus that the patient was admitted to the hospital.

Extension and Metastasis

Even if left to themselves, chondrosarcomas (central or peripheral) are likely to remain only locally invasive for years. After an initial surgical intervention, a local recurrence is certainly to be expected if the tumor has not been widely excised. Local recurrence of the lesion in even bulkier form is almost the rule at subsequent interventions under these circumstances. However, even then there may still be no definite spread of the growth for a long time, and death may take place from other causes. When a chondrosarcoma finally does spread, the tumor tends to break into the regional venous channels, and, by intravascular growth and extension, without necessarily adhering very much to the vessel walls, may reach the heart and lungs. Though it is ordinarily years before this occurs, in an occasional case the disorder runs its course so rapidly that the patient is dead within some months after the original tumor in the bone was first noted. The presence of severe respiratory and cardiac difficulties for a time before death in a patient with a chondrosarcoma may well be a clinical indication that cordlike intravascular growth and extension of the tumor to the heart and lungs has taken place.

A remarkable example of such neoplastic extension is the case, described by Ernst,[14] of a chondrosarcoma involving the lower part of the vertebral column. In this case there were tumor plugs in both the renal and the suprarenal veins, the left internal spermatic vein, the azygos vein, the inferior vena cava, the right auricle, and the branches of the right and left pulmonary arteries; and still the pulmonary parenchyma was free from metastases. Kósa [15] described a femoral chondrosarcoma with neoplastic extension to the homolateral femoral and iliac veins, the inferior vena cava, the right heart, and both branches of the pulmonary artery, even to the capillaries, again without the occurrence of any parenchymal metastases, even in the lungs.

In other cases, while extending into the large venous channels, the tumor also gives rise to parenchymal metastases, at least in the lungs. In the case described by Weber [16] there were metastases not only in the lungs but also in the liver (around tumor-plugged branches of the portal vein), but in the case reported by Warren [17] the metastases were limited to the lungs. Actually, metastases elsewhere than in the lungs

are uncommon in connection with chondrosarcomas. The possibility of lymphatic spread also exists, and extension of the tumor to lymph nodes, especially regional, has occasionally been reported. However, it is to be recognized that small secondary nodules of tumor not far from the primary mass might easily be wrongly interpreted as representing lymph nodes which have undergone complete replacement by tumor.

Microscopic Pathology

As noted, we used as a background for comparison in our study of chondrosarcoma 27 solitary benign enchondromas * and 50 solitary osteochondromas or osteocartilaginous exostoses. In regard to the enchondromas, apart from their gross features, it was found that they varied considerably in respect to cellularity, some being relatively rich in cells, others relatively poor, and still others showed intermingled areas of greater and lesser cellularity. (On the average, of course, they were definitely less cellular than chondrosarcomas.) Where the intercellular matrix was hyaline, the cells of enchondromas were usually roundish, but where the matrix appeared edematous or even mucoid, they tended no longer to be so, and their cytoplasm was likely to be multipolar or stellate. Some lesions or parts of lesions showed considerable or even heavy calcification of the intercellular matrix, and even some osseous metaplasia of heavily calcified areas.

However, it was found that in defending the benignity of an enchondroma, no great weight was to be attached to the relative cellularity, the distribution and shape of the cells, the presence or absence of lacunae about the cells, or the amount and character of the ground substance between the cells. Indeed, it became apparent that the picture of benignity is created by the characteristics of the cells themselves (as observed in viable and noncalcifying areas of the lesion) and specifically by the following features: (1) the component cartilage cells are fairly consistently rather small; (2) the vast majority of them have only one nucleus; (3) this nucleus tends strongly to be rather small and definitely not plump in relation to the cell as a whole; (4) such cells as are binuclear usually are still small, still have small (and also not plump) nuclei, and are found only occasionally and even then only in scattered fields; and (5) in particular there are no large or giant cartilage cells with large single or multiple nuclei or with clumps of chromatin. (See Figures 15 and 16, and compare with Figures 17, 18, 20, 24 and 25, for instance.)

* Since the present article was submitted, our material on the benign central cartilage growths has been published. See: Jaffe, H. L., and Lichtenstein, L. Solitary benign enchondroma of bone. *Arch. Surg.*, 1943, **46**, 480–493.

In regard to the osteochondromas, it is, of course, the status of the cartilage cap that is significant. This cap may or may not be still actively growing at the cartilage-bone junction and increasing the size of the osteochondroma at this site. Apart from the zone in which endochondral growth may thus be going on, and apart from areas which are undergoing calcification and ossification, the condition of the cartilage cells of the cap will be essentially like that noted as obtaining in benign enchondromas. If a growth zone is present in the deep part of the cap, the cartilage cells in that zone will be found lined up in short columns, enlarged, and even presenting significant numbers of plump, single or double nuclei. However, the whole cellular picture in such a zone of growth is an orderly one, corresponding to that seen, for instance, at the growing surface of an epiphyseal cartilage plate or in relation to cartilaginous callus, and hence not needing to be considered in judging the condition of the cap as a whole in respect to benignity. Indeed, in any focus of cartilage proliferation (for instance, even in a cartilaginous joint mouse) one can expect to find some cells of the type which, if observed in a cartilage tumor of bone, would make one view the lesion rather seriously. However, what we are saying about the cytologic diagnostic criteria applies, of course, only to the cartilage tumors.

In evaluating the cytology of a chondrosarcoma, as in evaluating that of an enchondroma or an osteochondroma, attention should likewise be concentrated solely upon areas which are viable and not heavily calcified or ossified. The reason is that in areas which are undergoing necrosis, heavy calcification, or ossification, the cartilage cells (and particularly their nuclei) are likely to be swollen because of these changes, that is, for reasons irrelevant to the benignity or malignity of the lesion. A chondrosarcoma may violate the histologic criteria of benignity to such an extent that even without knowing anything about the gross appearance of the lesion the examiner becomes aware of its malignity at a glance (Fig. 25). On the other hand, a chondrosarcoma may violate the criteria rather subtly and require, for its proper diagnosis, detailed scrutiny, under high magnification, of many microscopic fields, and more material than is ordinarily obtained for biopsy by a punch (Figs. 20, 21 and 23). When this is the case, the lesion is often "underdiagnosed" histologically, at least at first, as a benign enchondroma or osteochondroma, its chondrosarcomatous nature not being appreciated until a recurrence appears and perhaps reappears. We ourselves had originally "underdiagnosed" a number of our cases, as was borne in upon us by subsequent sad experience with them.

The case (Figs. 1 and 2) in which the lesion was in the upper end

of a humerus represented an instance of very early and subtle deviation in the direction of malignancy. Histologically, on the basis of the original biopsy, one could not have entertained, in this case, any other diagnosis than that of a benign enchondroma (Fig. 19). The cartilage of the resected specimen obtained 10 months later showed, especially in parts of the peripheral zone, an unequivocal change in the direction of malignancy. Specifically, as compared with those of the specimen taken for biopsy, the cartilage cells in these areas, though small on the whole, had plump nuclei. Furthermore, some fields, here and there, showed a significant sprinkling of cells with two or even four nuclei, and also a number of large cells, each of which had a large nucleus (Fig. 20).

The rather small peripheral chondrosarcoma developing out of an osteochondroma of a rib (Figs. 11 and 12) again shows the necessity of searching for, and paying close attention to, cytologic abnormalities which may not be obvious at first sight. In the wide cartilaginous cap the cells in this lesion, too, were, on the whole, somewhat plump, and in some areas more than a sprinkling of them were binuclear, while here and there some definitely large ones with single large nuclei were also encountered (Fig. 21). In the recurrence studied 3 years later, the lesion showed unmistakable histologic evidences of progression in malignity. Almost everywhere, but more definitely in some fields than in others, the lesion was very cellular and the cartilage cell nuclei were now plump, on the whole. Many more binuclear cells and many more large cartilage cells with single large nuclei were seen. This was the picture not only at the periphery of the recurrent lesion but to a very great extent in the cartilage lying among calcified cartilage and osseous material in the interior of the lesion.

In the case illustrated in Figures 3 and 4, ominous cytologic features were recognizable though not conspicuous in many areas of the amputated specimen, including curettings from the marrow cavity of the femoral stump (Fig. 23). They were very prominent in the disarticulated femoral stump, obtained 10 months later, which showed flowering of the lesion into an exuberant chondrosarcoma (Fig. 24).

Eventually, in a fully developed chondrosarcoma, central or peripheral, the neoplastic tissue is richly cellular. In addition, it shows striking irregularity in the size of the cells and their nuclei, the presence of numerous plump cells with multiple nuclei, pronounced hyperchromatism of the nuclei, and the presence of many uninuclear giant cells (Fig. 25). From lesion to lesion there are variations in detail. However, if material taken at different times is examined, the general cytologic picture of that particular lesion tends to remain more or less

consistent, though one can usually trace cytologically the progression of malignity from one examination to another.

In the histologic diagnosis of chondrosarcoma, not too much importance should be attached to the scarcity or even absence of mitotic division figures. If one concentrates attention upon these, one may miss the diagnosis, since cell division in chondrosarcomas tends to be amitotic. This does not mean that advanced chondrosarcomas may not show more than a sprinkling of mitotic division figures, but when they do, the histologic diagnosis is already obvious for other reasons.

Partial or extensive alteration in the character of the cartilage matrix—that is, change from hyaline to myxoid or mucoid—is not a particularly significant element in the composition of chondrosarcoma. It is true that, especially in the more bulky growths, larger or smaller areas of semisoft or gelatinous cartilage are likely to be found. However, these represent merely a nonspecific, secondary degenerative change whose incidental character is usually attested by the presence elsewhere of areas of hyaline cartilage. Chondrosarcomas which show extensive myxomatous degeneration are often designated as myxochondrosarcomas. It seems to us, however, that the prefix *myxo-* might well be dropped, even in these cases, since there appears to be no special reason for this emphasis on an aspect of the pathologic picture which is not distinctive and which has nothing to do with interpretation of the lesion in respect to malignity.

The presence, in a cartilaginous growth, of some, or even considerable, calcification and ossification is not inconsistent with its being a chondrosarcoma. In a central chondrosarcoma, such areas may be regarded merely as evidence that the growth had been benign in the past and that it had matured and regressed to some extent at some time before undergoing revivescence and malignant transformation. In a peripheral chondrosarcoma, some calcification and ossification of the matrix, at least in the early phases of the growth, are to be expected. They should not, though they often do, lead one to designate the lesion as a chondro-osteosarcoma or an osteochondrosarcoma and thus to imply that it represents a form of osteogenic sarcoma. Even if an osteochondroma is tending toward malignancy, it is in the nature of its proliferating cartilage cap to undergo calcification and ossification in the course of its development.

In relation to the microscopic diagnosis of chondrosarcoma, some consideration should be given to a tumor which we [18] have recently discussed under the heading of "benign chondroblastoma of bone." This tumor has usually been referred to as the "benign calcifying," or "epiphyseal chondromatous" giant cell tumor. It requires mention here

because it has sometimes also been regarded as a chondroblastic sarcoma or as a chondrosarcoma. As we have pointed out, however, though there is an aura of cartilage about the benign chondroblastoma, the latter is to be regarded as a specific type of tumor which cannot correctly be interpreted as a tumor of mature cartilage at all, and certainly not as a sarcomatous cartilage growth. The tumor cells of this lesion, which do not mature into full-fledged cartilage cells, should be interpreted, in our opinion, as chondroblasts, and the tumor itself as a chondroblastoma. The word "benign" was prefixed to indicate that the lesion is not a malignant one, despite its richly cellular character. Benign chondroblastoma starts its development in an epiphysis, usually of some long bone. It seems to predilect males, and the patients, in contrast to those with chondrosarcoma, are almost always adolescents or post-adolescents. The lesion is entirely benign and heals without recurrence after thorough curettage, even without supplementary radiation.

We have seen 3 examples of another lesion which seems also to require mention here but which we have great difficulty in classifying. It starts presumably as a focus of more or less collagenous connective tissue which undergoes myxomatous degeneration, and lends itself rather easily, even histologically, to confusion with chondrosarcoma. In 2 of the cases, the lesion was in a femur, at the lower end of the shaft, and in 1 in the proximal end of the shaft of a metatarsal bone. In all 3 cases, the lesion tended to be eccentric, bulged out the cortex in its vicinity, and appeared roentgenographically as a roundish, moderate-sized area of trabeculated rarefaction. Histologically, study of many fields from such a lesion shows residua of collagenous spindle-cell connective tissue in process of myxomatous degeneration (Fig. 26). In the clearly myxomatous areas, the cells show branching cytoplasmic processes and are separated by larger or smaller amounts of myxomatous basophilic cytoplasm. Some of these cells may even show retraction of these processes and come to lie in lacuna-like spaces. Particularly where the collagenous connective tissue is actively undergoing myxomatous degeneration, cells with very large hyperchromatic nuclei and cells with two, three, or more such nuclei may be numerous, and create the impression of tumor giant cells. In these areas, polymorphonuclear leukocytes are also to be seen. These lesions may also show areas of cystic degeneration and residua of hemorrhage, indicated by the presence of some foreign body giant cells and macrophages laden with hemosiderin.

Among the cases which Bloodgood [19] has described under the heading of "myxoma of bone" we find one in which the histologic picture

as reproduced photographically is exactly like that in these 3 cases which are puzzling us. In Bloodgood's case, there were a number of recurrences after curettage, thermal cautery and irradiation therapy, but though he gives a very somber prognosis in general for the lesion which he calls "myxoma of bone," the patient in this particular instance was still living and without metastasis more than 2 years after the original surgical intervention. In regard to our own cases we know that in spite of the ominous impression created by the histology of the lesion, mere curettement of it in two instances, and resection of it in one, was not followed by recurrence during a subsequent period of 2 years, 1 year, and 3½ years, respectively. We, ourselves, are not yet clear as to the proper classification of the lesion, and wish merely to record our findings in regard to it because of its superficial resemblance to chondrosarcoma.

Clinical Aspects

Age and Sex Incidence, and Localization

Most of the patients with chondrosarcoma have reached adulthood. In occasional instances, they are still in the teens, but in the great majority they are between 30 and 50 years of age. The disorder does not seem to predilect either sex. These generalizations, drawn from our relatively few cases, seem to be in line with what one can gather from the literature. In evaluating the latter, however, one must make due allowances for misclassification of cases. Many cases reported under the heading of chondroma turn out, on closer study of the report, to represent what is paradoxically labeled "recurrent chondroma" or "benign metastasizing chondroma," that is, actually chondrosarcoma. These considerations make it difficult also to estimate, from large numbers of cases, the true incidence and localization of chondrosarcoma. It appears, however, that the long tubular bones, the innominate bones, and the ribs, in descending order, are the most common sites.

Clinical Findings

In most of our cases the patients had already had a long but not dramatic history at the time of admission. This was true irrespective of the bone affected and of the central or peripheral origin of the chondrosarcoma. On the whole, the history tended to be longer in the cases of peripheral chondrosarcoma. Very short histories, associated with a fulminating clinical course, are clearly exceptional (though a few have been recorded) and we ourselves have observed no cases of this kind.

Thus in the case of peripheral chondrosarcoma which evolved from

a costal osteochondroma, the patient stated that for 12 years she had been aware of a painless mass which slowly grew to the size of an egg. In the case in which the chondrosarcoma (a huge one) developed from an osteochondroma of a tibia, the patient stated that for 24 years he had been conscious of a slowly enlarging, but certainly not disabling, tumor mass in the upper part of the leg. In our case of peripheral chondrosarcoma of an innominate bone there was an 8-year history of a slowly progressive tumorous enlargement associated with scarcely any clinical difficulty. Even in the case of multiple exostoses in which the chondrosarcoma developed on a rib, 2 years elapsed before the lesion had reached the size of a grapefruit and the need for treatment became urgent.

While, as noted, the histories in the cases of central chondrosarcoma tend to be somewhat shorter, yet it is not unusual, in such cases either, to get a history dating back 4 or 5 years. For instance, in one of the cases of central chondrosarcoma of a femur the patient stated that he had had dull, aching, local pains at intervals for 5 years, with some short-lived exacerbations. It was not until he accidentally palpated a mass along the lateral aspect of this femur that he sought medical care for his difficulty. On the other hand, in another case in which the chondrosarcoma was in a femur, the complaint was of only 6 months' standing. This patient gave a history of pain and functional disability in the region of the knee, worse at times, but never bad enough to confine him to bed. In one of the cases of central chondrosarcoma of an innominate bone, there was a history that for 5 years there had been moderate and intermittent pain and disability in the region of the homolateral hip joint, latterly associated with pains shooting down the entire leg. Local physical examination revealed the enlargement, slight to considerable, of the area affected. The enlarged part was firm or bone-hard, and usually not very tender, and the overlying skin was never red or warm. When the area involved was near a joint, the latter was likely to be found somewhat swollen and its motion somewhat restricted.

Trauma

We analyzed our cases as to the possible relation of a trauma to the development of the tumor. It is significant that in about half of the cases in which the data were adequate the patients stated definitely that they knew of no antecedent trauma which could have any bearing upon the lesion. Two patients in whom the chondrosarcoma developed in an osteochondroma stated that 24 and 8 years before, respectively, trauma led to discovery of a local tumescence which must have been

the osteochondroma. Whether this long-antecedent trauma instigated growth and transformation of the osteochondroma into a chondrosarcoma cannot be definitely known. Our cases include one osteochondroma undergoing slow transformation into a chondrosarcoma clearly without the agency of trauma. In fact, there was only 1 case among our 15 in which it was reasonable to suppose that trauma might have been a factor. This was the case of a man suffering from multiple exostoses who received a blow to one side of his chest and who, 6 months later, showed a definite and enlarging malignant tumor of a rib in the general region of the trauma. It should be borne in mind in this connection, however, that the natural tendency toward malignant transformation of an osteochondroma is stronger in cases of multiple than in those of solitary osteocartilaginous exostoses. Altogether then, even in those cases in which there seems to be a traumatic factor, it cannot be accepted without mental reservations.

Roentgenographic Findings

These may go far toward confirming the suspicion, perhaps already aroused by the history and physical findings, that one is dealing with a chondrosarcoma. Certainly, a long bone presenting an irregularly mottled and calcified shadow in its interior and a fuzzy area of localized destruction of the cortex should make one suspect tumor of this type (Fig. 4). This suspicion is all the more justified if, where the cortex is undergoing destruction, it is somewhat thickened in part or throughout, and is overlaid by tissue casting an abnormal shadow.

In the absence of mottling and calcification as a clue to the cartilaginous nature of a central bone lesion, it will not be clear at all that a given malignant tumor in a long bone is a chondrosarcoma (Fig. 9). For instance, in one of our cases, when first seen, the lesion presented itself as a somewhat trabeculated but not particularly radiolucent area involving the lower quarter of the shaft (which was slightly expanded), and part of the external condyle of a femur. Were it not for the fact that, in the affected area, the cortex, especially anteriorly, appeared fuzzy, apparently in consequence of invasion by tissue from the medullary cavity, one would have had good reason to interpret the lesion at this stage as benign and possibly as a large solitary focus of fibrous dysplasia.[20] Within a few months there could be no doubt that the lesion under consideration was a malignant tumor, for by that time the roentgenogram (Fig. 10) showed extensive destruction of the cortex and the presence of a large, extra-osseous tumor mass. Still, neither in this mass nor in the tumor within the bone were there mottled opacities suggesting a cartilage growth undergoing calcification and

ossification. Altogether, in this case, if one did arrive at a diagnosis of chondrosarcoma roentgenographically, this conclusion could have been reached only by the process of elimination.

The peripheral chondrosarcomas are, on the whole, not difficult to single out. A benign osteochondroma, whether small or large, presents roentgenographically a more or less uniform texture and a well defined peripheral outline, beyond which there are no abnormal shadows. In contrast, an osteochondroma which has undergone transformation into a chondrosarcoma presents a dense, blotchy appearance over a considerable area, usually associated with the presence of more ragged, irregular radiopaque streaks extending away from the main part of the lesion (Figs. 13 and 14).

Treatment

The only form of therapy which offers any prospect of cure in cases of chondrosarcoma is surgery. Irradiation therapy is hardly of any value, since this type of tumor is highly resistant to such treatment, tending to continue or resume its growth in spite of it. Irradiation may serve at most as a palliative agent for a chondrosarcoma in a site inaccessible to surgical intervention, and should not be used with any higher expectation.

Surgical treatment of chondrosarcoma should be definitely on the radical side, and the wider the margin of supposedly normal tissue the better. A radical procedure offers the best promise of success when it is undertaken at the initial intervention. For instance, if the tumor seems, clinically and roentgenographically, to be confined to the lower half of a femur, but the surgeon, on amputating, finds cartilage in the marrow cavity of the bone at a level which he had thought would clear the lesion, it will be advisable to disarticulate at the hip joint immediately, also removing as much of the capsule of the hip joint and overlying muscle and other soft tissues as is feasible. Otherwise, a recurrence in the amputation stump is almost inevitable, and when this has taken place disarticulation at the hip joint is very likely to be too late to save the patient. As a part of the general principle of giving the lesion a wide margin in any site, the policy of keeping one joint ahead of the growth is a valuable one. Indeed, in connection with chondrosarcoma of one of the bones of the foot, for instance, it is advisable to amputate above the ankle joint rather than to attempt excision. On the same basis, if the lesion is in a rib, certainly several inches of the rib on each side beyond the region of apparent involvement, and at least corresponding sections of the rib above and below the affected one, should be sacrificed. The hopeful aspect of radical

surgery (and specifically of the prevention of recurrence by keeping well ahead of the growth) in cases of chondrosarcoma lies in the fact that as a rule the tumor has not yet metastasized at the time of the initial surgical intervention.

Summary and Conclusions

Chondrosarcoma is to be regarded as a lesion distinct from osteogenic sarcoma of bone. The former develops out of full-fledged cartilage, while the latter issues from more primitive tissue, developing out of bone-forming mesenchyme. Some chondrosarcomas do show large areas in which the intercellular matrix of the tumor cartilage has become heavily calcified or ossified, and in some osteogenic sarcomas cartilage in considerable amounts may be formed in the course of osteogenesis from the primitive mesenchyme. However, in a chondrosarcoma, in contrast to an osteogenic sarcoma, one never sees tumorous osteoid tissue and bone which is evolving out of a sarcomatous stroma directly, such as one always sees somewhere in an osteogenic sarcoma, no matter how much cartilage it contains.

In comparison with osteogenic sarcoma, chondrosarcoma is definitely less common, appears at a later age (on the average), runs a much slower course, and, especially if given radical surgical treatment at an early stage, has a much better prognosis, since the tumor has usually not yet metastasized at the time of initial surgical intervention. Even when the tumor is inadequately extirpated, it tends to recur only locally one or more times before extending to the tributary veins or to the lungs. Local trauma does not seem to be a factor in the initiation of chondrosarcoma or in the malignant transformation of the benign growths (enchondroma and osteochondroma) from which chondrosarcomas so often evolve.

A chondrosarcoma which begins its development within the interior of a bone may be denoted as a central chondrosarcoma, and one which begins in the cartilaginous cap of an osteochondroma as a peripheral chondrosarcoma. It is in the peripheral chondrosarcomas and those central ones which have clearly evolved from benign enchondromas that one finds, at least in the earlier stages of evolution of the lesion, heavy calcification or ossification of large parts of the intercellular matrix of the tumor cartilage. In other chondrosarcomas the relevant neoplastic tissue is likely to consist, in the main, of compacted islands of cartilage with hyaline matrix, though if the chondrosarcoma is very bulky one may also see areas in which the cartilage is softer and myxomatous, and perhaps even necrotic.

Although it is true that the histologic picture of a particular lesion

(irrespective of its gross appearance) does not have to be crudely and obviously sarcomatous to indicate chondrosarcoma, yet it is a mistake to suppose that to make a diagnosis of chondrosarcoma on a histologic basis alone is often difficult if not impossible. We think we have made it sufficiently clear that, even in the early stages of the evolution of a chondrosarcoma, one will find, at least in scattered fields, if adequate material is examined, subtle but tell-tale evidences of cytologic atypism of the cartilage cells which will betray the malignant character of the lesion. We hold that a cartilage tumor should no longer be regarded as benign if, when viable and not heavily calcified areas are examined, it shows, even in scattered fields: (1) many cells with plump nuclei; (2) more than an occasional cell with two such nuclei, and especially (3) any giant cartilage cells with large single or multiple nuclei or with clumps of chromatin. We feel that, by observing these criteria, the prevalent tendency to "underdiagnosis" of chondrosarcoma in an early stage of malignancy can be overcome. In a more fully evolved chondrosarcoma these indications will be relatively easy to find if one recognizes their diagnostic importance, and in a fully developed chondrosarcoma, of course, the histologic picture may even be obviously sarcomatous.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

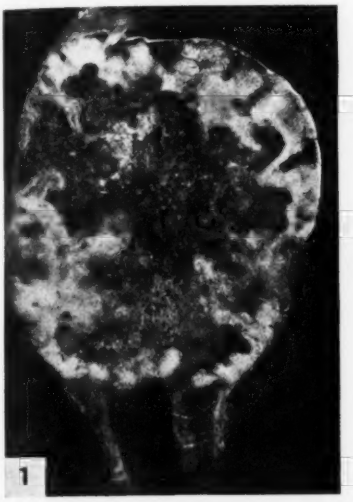
PLATE 63

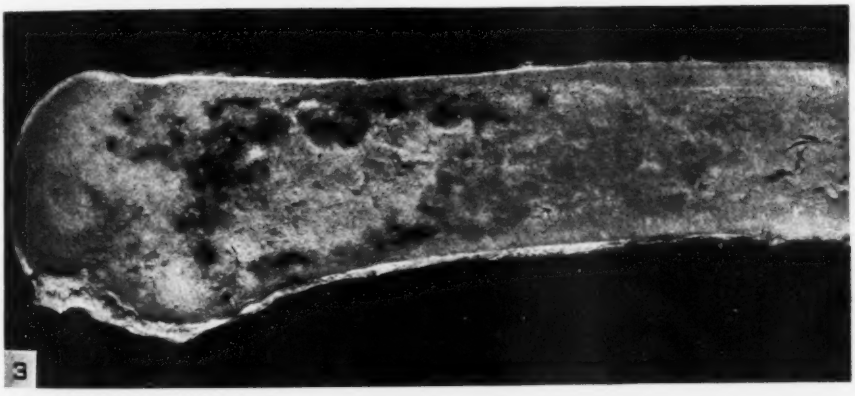
FIG. 1. Photograph showing sagittally cut surface of an upper end of a humerus presenting a chondrosarcoma early in the course of its evolution from a calcified and ossified enchondroma. It can be seen that the surgical and anatomic neck of the bone is somewhat expanded, and there are also indications that the articular surface is finely ridged and knobbed. Small foci of cartilage can be seen in the central part of the affected area, though on the whole this part is osseous. Peripherally, a cuff of hyaline cartilage of irregular thickness can be noted, and it was certain areas of this cuff that revealed the sarcomatous character of the lesion histologically. The periosteum has not yet been perforated at any point. (See Fig. 2 for roentgenographic, and Figs. 19 and 20 for cytologic features of this case.)

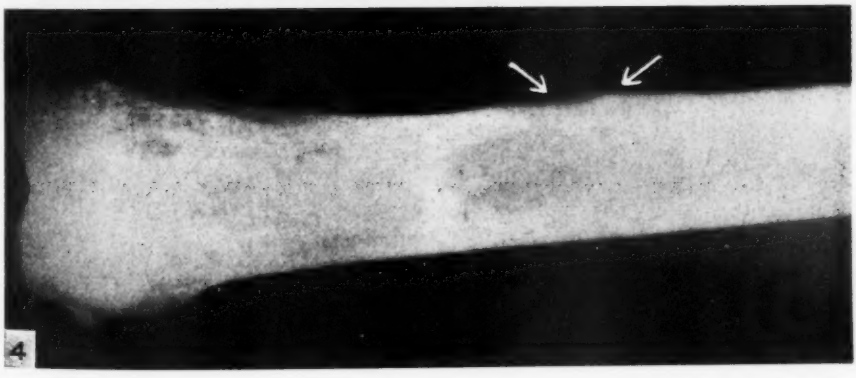
FIG. 2. Roentgenograph of the affected portion of the humerus shown in Figure 1. The relative radiolucency at the periphery reflects the peripheral cuff of hyaline cartilage. The relative radiopacity and stippled appearance of the central part reflects calcification and ossification apparently dating back to the benign enchondromatous stage of the lesion.

FIG. 3. Photograph showing sagittally cut surface of a portion of a femur with a chondrosarcoma which likewise appears to have evolved from a calcified and ossified benign enchondroma. The ablated portion of the femur showed no alteration in contour, except for the presence of a small tumescence anterolaterally (not demonstrated in the present photograph) at about the junction of the lower and middle thirds. The sectioned specimen revealed the presence, in the medullary cavity, of areas of white, glistening, and clearly cartilaginous tissue, alternating with areas of heavily calcified cartilage, along with a few areas which seemed to represent foci of ossification developing in such cartilage. By appropriate transverse sectioning of that half of the specimen which showed the mass mentioned above, it was found that in the area in question the cortex had been perforated by cartilage growing through at several points from the medullary cavity. (See Fig. 4 for roentgenographic, and Figs. 23 and 24 for cytologic features of this case.)

FIG. 4. Roentgenograph (preoperative) of femur from the case illustrated in Figure 3. There is a radiopaque mottled shadow filling the interior of the bone and reflecting the presence of considerable calcification and ossification of the tumor. There is no alteration in the contour of the bone and no thickening of the cortex, except where the latter has been perforated (see arrows).







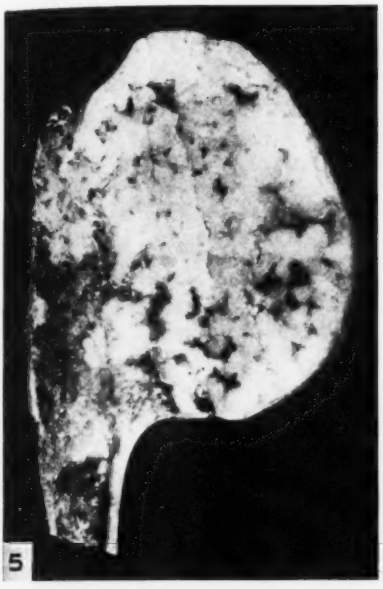
Lichtenstein and Jaffe Chondrosarcoma of Bone

PLATE 64

FIG. 5. The coronally cut surface of the lower end of an ulna with chondrosarcoma from a case of enchondromatosis involving also the homolateral radius and many of the bones of the corresponding hand. The ulnar lesion, as well as the lesions in the fourth finger, had shown a recent pronounced exacerbation of growth and had transgressed the original boundaries of the bones. The affected ulnar area and finger had therefore been resected. In the ulna may be seen compacted facets of hyaline cartilage composing the main mass of the tumor and continuous with the cartilage of the interior of the bone shaft. The scattered dark spots are foci of ossification, many of which are distributed through the entire lesion and which show up en masse in the roentgenograph of this specimen (Fig. 6). That this lesion was a chondrosarcoma was clear histologically, but there has been no recurrence during the 2 years since resection was done. Lesions such as this one in the ulna, in cases of enchondromatosis, are often misdiagnosed, at least roentgenographically, as osteochondromata. It is for this reason that one finds statements in the literature to the effect that, in some cases of multiple enchondromatosis, multiple osteochondromata are also present.

FIG. 6. Roentgenograph of specimen illustrated in Figure 5.

FIG. 7. The sagittally cut surface of a femur presenting a chondrosarcoma. The neoplastic tissue, though clearly present within the major marrow cavity and the marrow spaces of the spongiosa of the affected portion of the femur, has broken out of the bone without distending it and grown mainly in the surrounding soft parts. The neoplastic tissue appears whitish and glistening and was composed of smaller or larger facets of cartilage, separated by thin connective tissue septa. The tumor infiltrates a good part of the capsule of the knee joint, especially posteriorly. The large arteries and veins behind the knee were compressed, but no neoplastic tissue was found adherent to the walls of the veins. The patient in this case died at another hospital 7 years after the amputation, but no autopsy was secured. (See Fig. 17 for cytologic features.)



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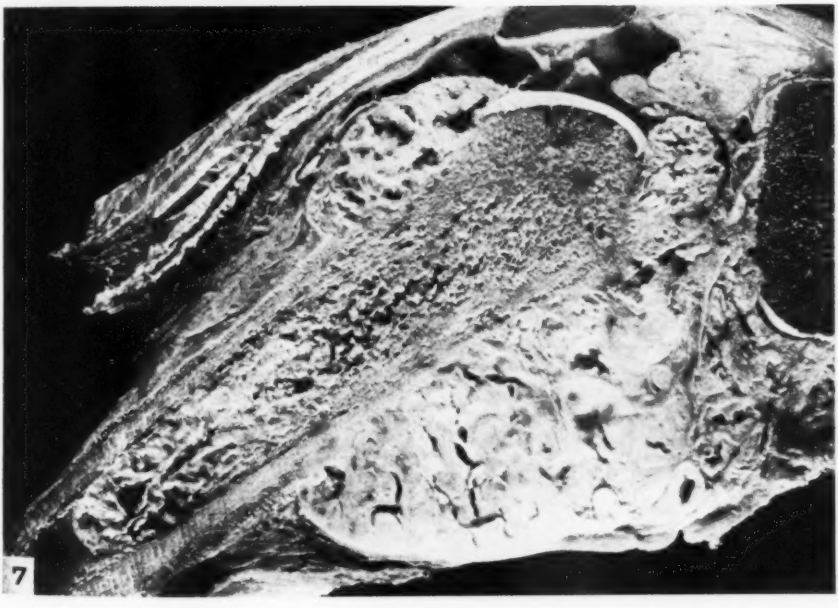

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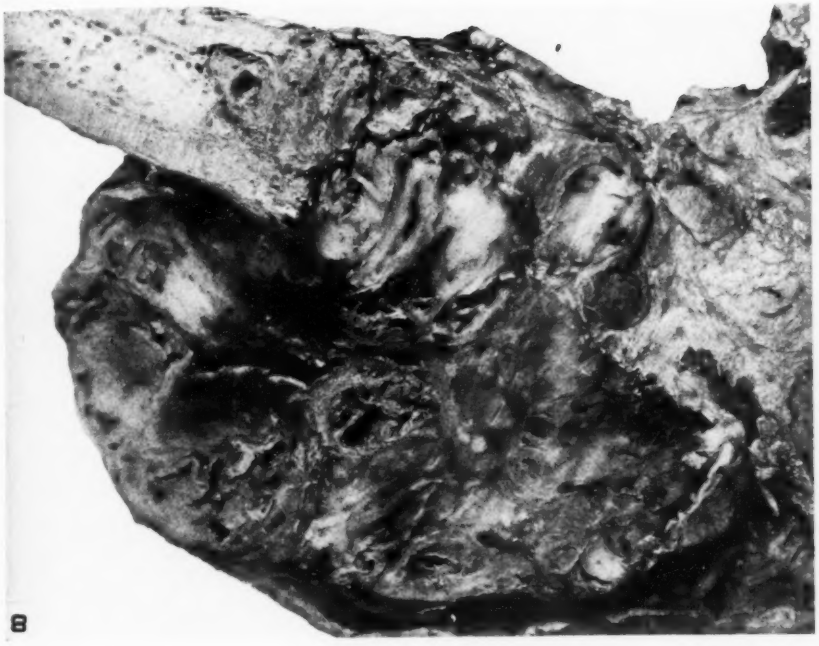
Lichtenstein and Jaffe Chondrosarcoma of Bone

PLATE 65

FIG. 8. The sagittally cut surface of a portion of a femur presenting a chondrosarcoma. There is extensive destruction of the affected area of the bone, and bulging of the tumor mass anteriorly and into the joint cavity. A neoplastic fracture is obvious somewhat above the femoral condyles. The sectioned specimen revealed, over most of its surface, soft, glistening, whitish cartilage which in some places had an almost myxoid consistency while in others it was more or less divided into facets by septa. Hemorrhagically discolored areas were also present, as were areas which appeared necrotic and softened, apparently in consequence of the heavy irradiation therapy which had been given without influencing the continued growth of the lesion over a period of about 8 months. Nowhere was the neoplastic tissue calcified and ossified. The large veins draining the affected area did not show any tumor thrombi. (See Figs. 9 and 10 for roentgenographic, and Fig. 18 for cytologic features.)

FIG. 9. Initial roentgenograph, taken 8½ months before amputation, of the lesion illustrated in Figure 8. On the basis of this roentgenograph, the lesion had been interpreted clinically as a giant cell tumor. The chondrosarcoma appears as a trabeculated rarefaction shadow and the cortex anteriorly is fuzzy and obviously in process of destruction. If there had been tell-tale spots of radiopacity reflecting calcification and ossification, the lesion could have been identified, clinically at least, as some sort of central cartilaginous growth.

FIG. 10. Roentgenograph taken 7½ months after that shown in Figure 9, and 1 month before amputation. The progression of bone destruction in spite of irradiation therapy is apparent. The extensiveness of the lesion beyond the limits of the bone does not stand out, because of the absence of calcification and ossification in the neoplastic cartilage.



Lichtenstein and Jaffe Chondrosarcoma of Bone

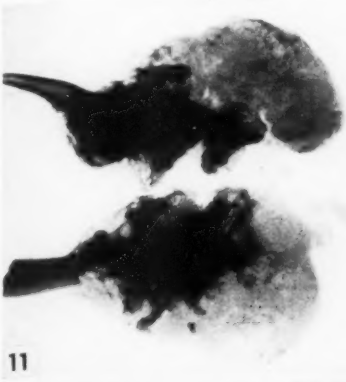
PLATE 66

FIG. 11. Roentgenograph of both halves of the sternal end of a rib sectioned in its long axis, presenting a chondrosarcoma which had developed from an osteochondroma. The more radiolucent part represents the wide cartilage cap of the lesion, while the deeply radiopaque area represents the heavily calcified and ossified portion. (See Fig. 12 for the gross picture.)

FIG. 12. The cut surface of the upper half of the lesion shown roentgenographically in Figure 11. The photograph was made after the specimen had been in a fixative for years but one can still see, near the middle of the specimen, a white and gray speckled core representing the gritty, calcified and ossified portion of the lesion. To the right, this was capped by a wide zone of hyaline cartilage, which, at its widest, was as much as 1.5 cm. thick. (See Figs. 21 and 22 for cytologic features.)

FIG. 13. Roentgenograph of a chondrosarcoma springing from a sixth rib in a case of multiple exostoses. The shadow cast by the tumor is mottled but, on the whole, radiopaque, reflecting extensive calcification and ossification in it. In this picture, important details relating to the external periphery of the tumor are lost because in this reproduction the lesion appears only about one-third as large as in the original roentgenograph. In the latter, it could be clearly seen that at the external periphery of the lesion the areas of radiopacity fade out into a wide zone of radiolucent tissue representing tumor cartilage which has not yet become calcified. Such a picture is characteristic of a chondrosarcoma developing from an osteochondroma. (See Fig. 25 for cytologic features.)

FIG. 14. Roentgenograph (anteroposterior and oblique views) of a chondrosarcoma evolving from an osteochondroma at the upper end of a tibia. The areas of radiopacity indicate calcification and ossification in the tumor. In the upper part of the oblique view there are ragged, irregular radiopaque streaks extending from the main part of the lesion, which are due to strands of calcification and ossification in the tumor cartilage.



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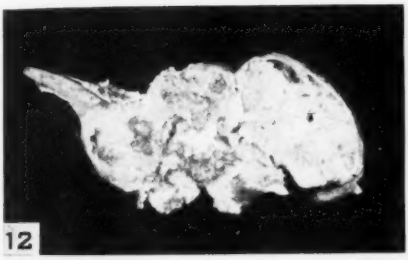

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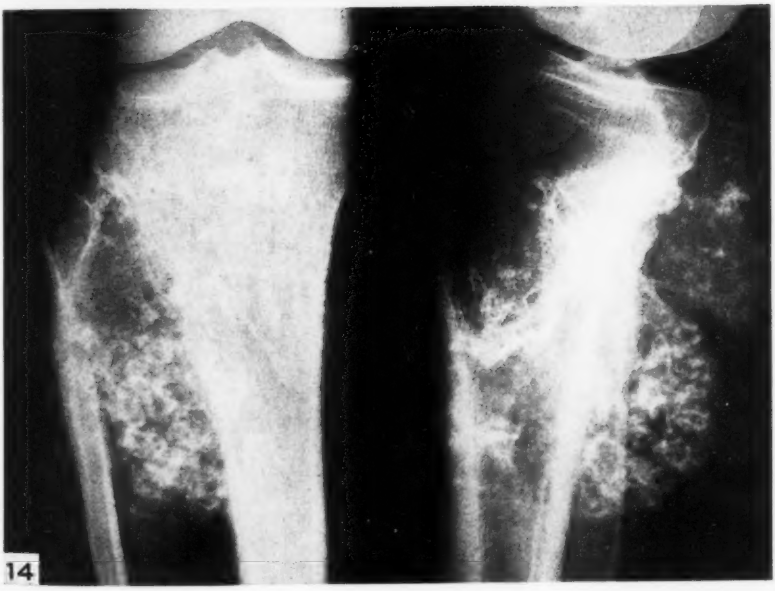

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Lichtenstein and Jaffe Chondrosarcoma of Bone

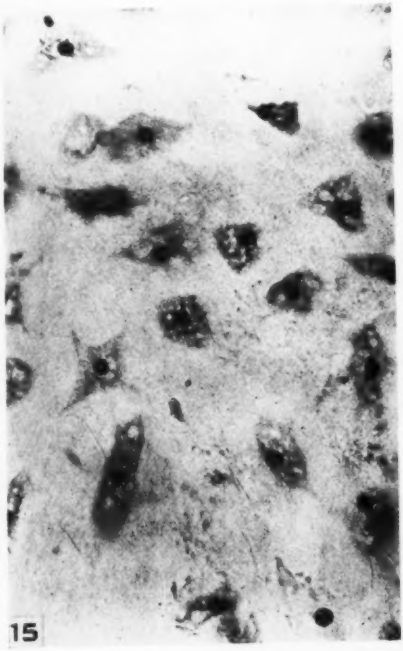
PLATE 67

FIG. 15. The histologic pattern of a typical field from a benign enchondroma. There are not very many cells in the field. The hazy and blurry appearance of the intercellular material is due to the presence of calcareous dust in it. Indeed, it is difficult to find, in a benign enchondroma, a field in which the intercellular material does not contain calcium, at least in the form of such tiny particles. The nuclei, though prominent, are small, especially in relation to the size of the cell as a whole. No cells with double nuclei are seen. × 250.

FIG. 16. The histologic pattern of a typical field from another benign enchondroma. Here the calcareous dust particles in the interstitial material are more abundant. Many of the cells have retracted in their lacunae, and in many both nucleus and cytoplasm appear drawn out. Again there are clearly no cells with double nuclei. × 250.

FIG. 17. The histologic pattern of a field typical of the viable tumor areas in the amputated specimen of the chondrosarcoma shown in Figure 7. At least five cells with double nuclei can be seen. On the whole, the nuclei here are much more prominent than those in Figures 15 and 16. × 250.

FIG. 18. The histologic pattern of a field typical of the viable tumor areas in the amputated specimen of the chondrosarcoma illustrated in Figure 8. The high cellularity of this tumor field is evident, and the nuclei tend to fill out the cells. Cells having two nuclei are numerous. × 250.



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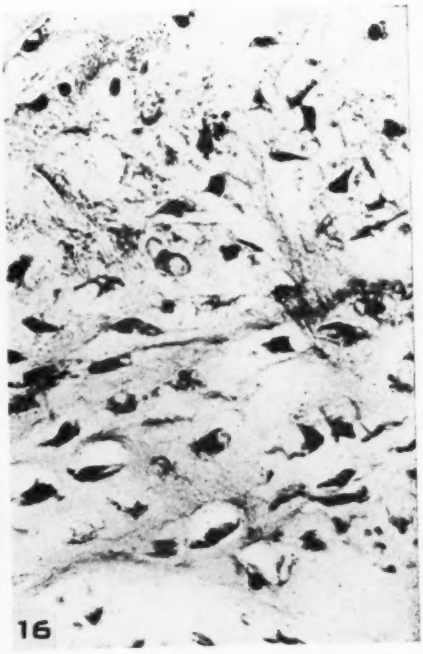

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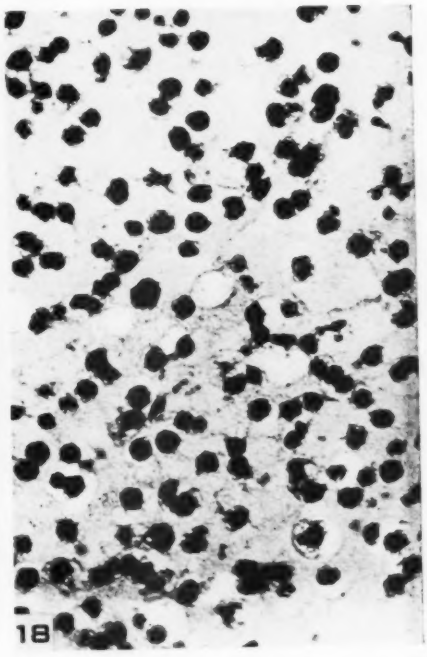

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Chondrosarcoma of Bone

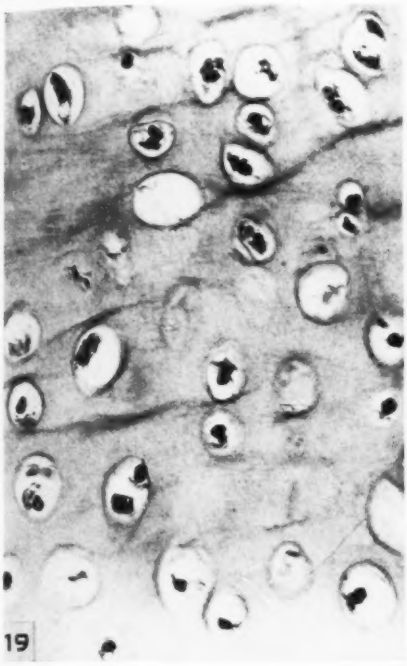
PLATE 68

FIG. 19. The histologic pattern of a typical field from the original specimen obtained for biopsy 10 months before the tumor illustrated in Figures 1 and 2 had been resected. On the basis of the histologic findings at that time, as shown here, the lesion was regarded as a benign enchondroma. The cells are relatively few, and lie retracted in lacunae; the nuclei are relatively small, and apparently only one cell is binuclear. × 250.

FIG. 20. The histologic pattern in scattered fields of the resected specimen illustrated in Figures 1 and 2. (Compare also with Fig. 19.) Now, 10 months after the original biopsy, the ominous fields are relatively more cellular and show many cells with two and even some with four nuclei. On the basis of even scattered fields like this, the lesion can be regarded as definitely a sarcoma. × 250.

FIG. 21. The histologic pattern of some fields in the cartilage cap of the lesion illustrated in Figures 11 and 12. On the basis of such fields, and particularly because of the presence of relatively many cells with two nuclei, the lesion, even at this stage, must be interpreted as a chondrosarcoma and a recurrence is certainly to be expected unless the lesion is very widely excised. The lesion did recur (see Fig. 22). × 250.

FIG. 22. The histologic pattern in the recurrence of the chondrosarcoma illustrated in Figure 21. There is now a great increase in cellularity, cells with double nuclei are numerous, and there are many cells with very large single nuclei. × 250.



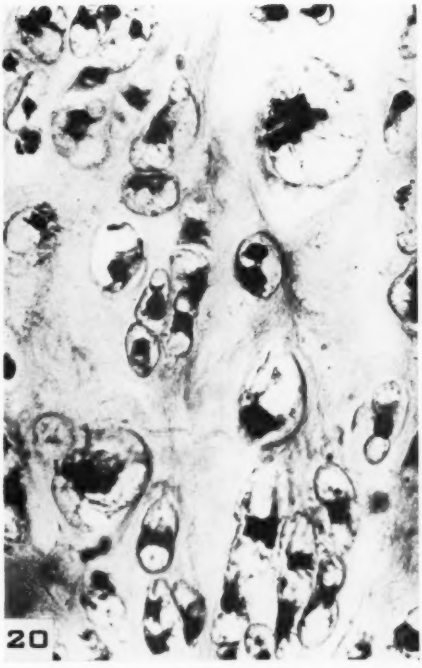


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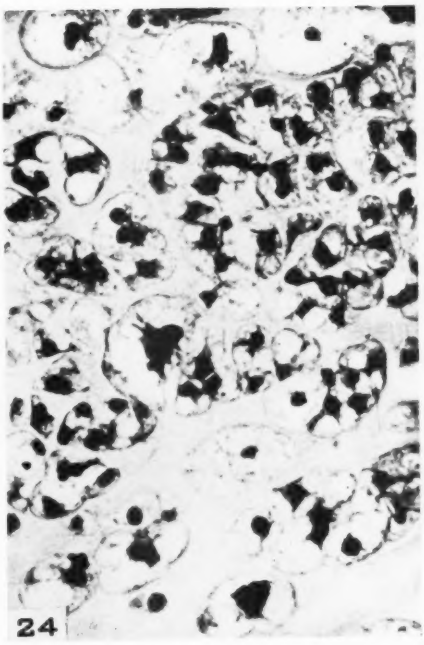
PLATE 69

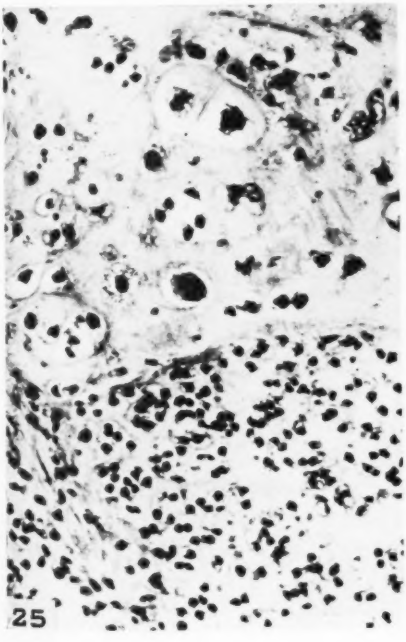
FIG. 23. The histologic pattern typical for fields in the area of perforation and for scattered fields in the cartilage within the medullary cavity of the amputated portion of the femur and in the curettings from the femoral stump in the case illustrated in Figure 3. On the basis of such fields, the lesion must be regarded as a chondrosarcoma and recurrence expected, since cartilage of this character had remained in the femoral stump. (See Fig. 24 for the histologic character of the recurrence.) × 250.

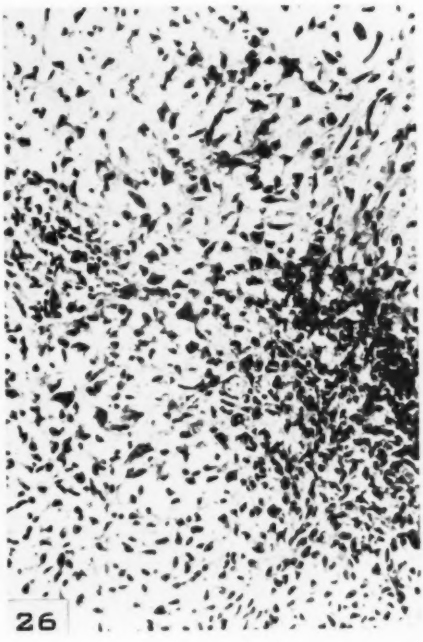
FIG. 24. The histologic pattern, typical for all viable areas, of the recurrence in the femoral stump of the chondrosarcoma illustrated in Figure 3. One finds now pronounced cellularity of the tumor cartilage and numerous binuclear cells. × 250.

FIG. 25. The histologic pattern, for all viable areas, of the large chondrosarcomatous tumor mass encasing the lung and found at autopsy in the case illustrated in Figure 13. The original neoplastic tissue obtained at resection of the affected rib in this case presented, on the whole, a cytologic character like that shown in the lower half of the present figure. Even at this relatively low magnification, many binuclear cells can be seen in this half of the picture. In the upper half, many giant cartilage cells with large nuclei are to be seen. Altogether, this picture is one of a fully developed chondrosarcoma. × 100.

FIG. 26. The histologic pattern of a tumor composed of collagenous spindle-celled connective tissue which is undergoing myxomatous degeneration. At first glance, and uncritically, one might regard this tissue as from a chondrosarcoma. × 100.







Lichtenstein and Jaffe Chondrosarcoma of Bone

TUMORS OF SWEAT GLANDS *

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A. HYPERTROPHY, HYPERPLASIA AND METAPLASIA

The sweat gland, unlike the sebaceous gland, seldom shows hypertrophy or hyperplasia as a primary change, but does do so as a process secondary to such lesions as nevi, angiomas, or hydradenoma ‡ papilliferum.[1-3] In some instances hyperplasia may suggest neoplasia. In Figure 2, there is shown hyperplasia of the secretory portion of the gland. This represents one of several hyperplastic glands which formed a tumor-like enlargement on the abdominal wall of a middle-aged woman. Cystic dilatation combined with the hyperplasia in some glands made the resemblance to neoplasia even more striking.

An unusual multiplication of glands is shown in Figure 1. The specimen came from the occipital region of a child, 5 years old, and had been present since birth.

A remarkable case was reported by Stokes [4] of a girl, 19 years old, who had marked enlargement and pigmentation of her leg due to a diffuse congenital angioma and a hyperplasia of the sweat glands associated with hyperhydrosis. The angioma responded to x-ray treatment but the sweat glands were unaffected.

Epithelial metaplasia, commonly associated with chronic irritation, is only occasionally seen in sweat glands although they are frequently irritated or inflamed. This may be related to the constant drainage of the glands.

We have noted single apocrine-like structures among coil glands, associated with chronic inflammation, on parts of the body where apocrine glands do not usually occur. It is a question whether this represents changed epithelium of sweat glands under abnormal conditions and, if so, whether it is properly considered a metaplastic change. In Figure 3 we present an example of metaplasia of the secretory alveoli in an inflammatory lesion of the hand.

Walther and Montgomery [5] reported metaplasia of the ducts in a palm of a woman, 29 years old, associated with nonspecific dermatitis and deep discharging fissures, present since birth. The metaplastic

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‡ The spelling "hydradenoma" is sanctioned by general usage. However, the correct form is "hidradenoma" since the derivation should be considered as from ἱδρώς (sweat) and not from ὑδωρ (water).

dilated ducts showed both mucus and keratin; the secreting portions of the glands were normal.

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B. Tumors of True Sweat Glands

The approach to tumors of sweat glands has been scholastic for so long that a consideration of the literature forms a necessary part of a report on the subject. This is illustrated by the introduction to the section on sweat glands in a recognized textbook.[61] "The reader is earnestly advised to refer to the literature given at the end of this chapter in order to acquaint himself in detail with this difficult part of dermatological histology." To this we demur. The literature is confusing and largely casuistic but we feel that more critical observation of the tumors will bring out only those difficulties attendant on the interpretation of any neoplastic process. Borderlines between hyperplasia, benign tumor, or malignant tumor are always problematical and questions of etiology may be as yet unanswerable.

In the early literature there were three main controversial points in differentiation of tumors of sweat glands: (1) distinction from tumors of other structures; (2) differentiation from hyperplasia of the glands; (3) recognition of tumors developing from the secretory and from the ductal portions of the gland.

The tumors of sweat glands were at first confused with endotheliomas and angiomas, as were all the nonkeratinized epitheliomas of the skin. Their peculiar tubular structure and the multiplicity of lesions set them apart as "hemangio-endothelioma tuberosum multiplex" [50] and "lymphangioma tuberosum multiplex." [52] Lotzbeck [58] in 1859 reported a tumor that he believed to be of sweat gland origin. Unna [95] accepted the author's interpretation, although he stated that Virchow considered the tumor angiomatous. On the other hand, some tumors that Unna attributed to sweat glands seem to us doubtful and might well pass for glomus tumors.[11, 47]

The differentiation between hyperplasia and neoplasia received much attention from the first observers of changes in sweat glands.[90, 95] The adenoma sudoriparum described by Verneuil [96] and other French writers was criticized by Unna [95] as including nonneoplastic changes. The many varieties of tumor-like proliferation of the glands described in the literature all show loss of normal architecture in a greater or less degree. A slight epithelial proliferation of sweat glands is not unusual, but increase in the number of glands as well is not commonly recognized. We have seen only one example of proliferation of glands in which the alveolar structure closely resembled the normal gland, while the diffuse nature of the growth and cystic dilatation suggested neoplasia.

The early classifications were concerned especially with the part of the gland involved in the neoplastic process—the secretory alveolus or duct. These two parts of the gland are distinguished by the appearance and arrangement of the epithelial cells and by the myoepithelium around the secretory alveoli. The differences in the epithelium are so slight as to be readily lost with abnormal proliferation. The myoepithelium, normally quite easily seen, is rarely recognized in tumors.[52, 60, 84] Both Buxton [7] and Unna [95] gave careful descriptions of tumors arising from the two parts of the gland. Unna considered them distinct on the basis of etiology. The spiradenoma,[2, 90] or tumor of secretory alveoli, he described as secondary to other lesions of the skin such as carcinoma, angioma, or varices, while the tumor of ducts, the syringadenoma, he interpreted as being congenital since it often appeared early in life and was not obviously associated with other conditions. Nevertheless, he granted the almost complete similarity of appearance except for hyaline or horny material present in cysts of the syringadenoma. The distinction between the spiradenoma and syringadenoma is now seldom made.

The origin of the tumors was stressed in the early classifications.[74, 86] But the factors on which the decisions were based, the relation of the tumor with other structures of the skin, the presence of secretion within the tumor, the status of adjacent sweat glands, their presence, absence, or abnormality, led to a diversity of interpretations.

In spite of a number of case reports and several more or less complete reviews in the past 40 years,[57, 77] the tumors are still ill-defined. The terminology of the early reports is only slightly modified today, and carries some of the uncertainty of the first observers. This is in part due to the comparative rarity and benignity of the tumors and to the absence of distinguishing clinical features.[16, 69] The tumors are slowly growing but may become very large. They are either mul-

tiple or solitary and may appear at any time of life, although a great majority arise in youth or on maturity. Some types are clearly congenital. Ulceration is unusual. They have been described on every part of the body, but some forms are common on the chest, others on the vulva, and others on the upper face around the eyes and scalp. The hands and feet are not unusual sites. An accurate clinical diagnosis is difficult with the exception of the types which have a typical distribution such as the syringoma of the chest and the hydradenoma of the vulva. Knowledge of the structure has been restricted because biopsy or treatment is seldom indicated.

We propose to correlate our experience with the literature. We recognize four types of tumors of sweat glands having distinctive patterns: (1) syringoma; (2) hydradenoma papilliferum; (3) hydradenoma; (4) hydradenoid carcinoma. Our terminology has been chosen with regard to histologic suitability and historical and clinical usage. We will give a brief gross and a rather more detailed histologic description, a discussion of the synonomy and an illustrative photomicrograph for each group.

1. *Syringoma*

This tumor is typically small, under 1 cm. in diameter, and multiple; but an occasional solitary tumor may be three or four times as large. It is slightly elevated, smooth, semitranslucent and colorless or slightly discolored. This condition affects females especially at puberty but it may appear first in middle life. There is some disagreement as to the usual distribution of the tumors, because of their close resemblance to epithelioma adenoides cysticum * (except for a less yellow color),[95] but it is probable that the latter is more often found on the center of the face and lower eyelids and the syringoma on the chest and axilla. Feit and Kelley[30] described a case with lesions distributed on the lower torso and thighs. Ullmo[94] reported a very curious case: a woman of 35 years, on becoming pregnant, developed hundreds of small, rounded, pinkish papules over the skin of the chest, neck, axillae and breast. There were no illustrations, but the descriptions correspond with our syringoma. These tumors are radiosensitive.[37, 45, 67]

The microscopic structure consists of epithelial groups scattered haphazardly through the corium usually without appreciable disorganization of the general architecture of the dermis. The separate unit

* A discussion of epithelioma adenoides cysticum may be found in our paper on epithelial cysts and cystic tumors of the skin to be published in the September issue of the Journal.

is a fairly short, narrow, sometimes branching strand of epithelial cells about the diameter of a normal coil duct, which it closely resembles. Cystic expansion, apparently the result of degeneration, adds to the similarity. The absence of myoepithelium [60] suggests origin from the ducts rather than the coils. The cysts are lined by cuboidal or flattened cells and contain clear fluid or hyaline or, rarely, horny material. Some authors have assumed that the fluid is the product of secretion. There may be a distinct basement membrane.

Civatte and Chevallier [14] described a lesion of unusual type, possibly belonging to this group. A number of subcutaneous lesions on the breast of a woman, 19 years old, were formed of discrete collections of sweat glands and dense fibrous tissue in the nature of a fibroadenoma. The report was not illustrated and it is difficult to be sure of their exact nature.

The sweat glands adjacent to the tumor may be normal, absent, or abnormal. Török [92] and Unna [95] stressed the absence of normal sweat glands in the vicinity of the tumor as evidence bearing on their congenital origin. Petersen,[72] in 1893, finally concluded that a tumor which he had previously reported [73] in 1892 as congenital, was from fully developed sweat glands. Edel [25] demonstrated syringoma developing from apparently normal ducts. The most commonly held view is that the tumor originates from embryonic sweat glands [16, 75, 101] and either grows slowly or not at all until puberty or later. A few writers have regarded these tumors as nevi of apocrine gland origin.[100]

We have only one tumor that may possibly belong to this class, although the clinical features were unusual. It came from the scalp of a male, 26 years old. It measured 0.8 cm. in diameter and had been noticed for only 3 months. The histologic structure was quite typical, however, except for a nodular grouping of the individual epithelial units and a rather prominent mucinous change in the stroma.

The tumor is known by several different names:

1. Syringoma or syringadenoma (Dohi,[20] Eller,[27] Gans,[39] Unna [95])
2. Syringocystadenoma (McCarthy,[61] Sutton and Sutton,[88] Török[92])
3. Syringcystoma (Finnerud,[33] White [103])
4. Hydradénome éruptif (Jacquet and Darier [49])
5. Cellules epitheliales éruptifs (Quinquaud [75])
6. Lymphangioma tuberosum multiplex (Kaposi [52])
7. Hemangio-endothelioma tuberosum multiplex (Jarisch [50])
8. Spiradenoma (Ewing [29])
9. Naevi cystepitheliomatosi disseminati (Pernet [71])

2. *Hydradenoma Papilliferum*

Hydradenoma papilliferum is a papillary growth of quite variable structure. It is particularly common on the labia, perineum and thighs,[4, 6, 26, 46, 62, 89, 108] but also occurs on the face, especially the upper lip, and on the scalp. It is more apt to be solitary than multiple, usually is noticed in middle life and grows slowly, but is generally not more than 2 cm. in diameter. The histologic structure is essentially papillary, expansile and discrete, but not encapsulated, and varies according to the complexity of the papillary ramifications, the proportion of solid growth, the tendency to degeneration and the amount of stroma. The epithelium is two-layered, the cells bordering the lumen are high-columnar. The nucleus has a central or basal position and the cytoplasm is typically faintly bluish or colorless. But it is not unusual to find here and there groups of rather squat eosinophilic epithelial cells reminiscent of apocrine glands. The papillae may be narrow papillary folds projecting into cystic spaces or complex, branching, intracystic growths. In the nonpapillary parts, the cells may form a loose mesh of glandular spaces with almost no stroma or they are closely packed together in a patternless mass. These latter seem to be formed in some instances by proliferation of basal cells of the ducts. Mitotic figures are not particularly numerous and there is rarely any appreciable degree of anaplasia. Cysts are formed in two ways: by growth and dilatation of the gland, and by degeneration within the tumor. A marked degree of necrosis is unusual. In a few tumors with predominant stroma, the cysts are stretched into cleft-like spaces and the resemblance to adenofibroma of the breast is striking. The growth may be completely intracystic. Many of the tumors arise in the lower corium or subcutaneous tissue. Not infrequently the tumor extends through the whole thickness of the corium. Rarely the tumor arises very near the epidermis. It has been surmised that the tumor arises from the duct. The epithelium is not characteristic of either part of the gland and the absence of typical myoepithelium probably is not significant.

Very few of the early writers considered this type of tumor in a separate category. We assume that it has been classed with nevi of sweat glands,[27] *i.e.*, either as naevus syringadenomatosus or as naevus syringocystadenoma papilliferus. Pick's [74] illustration (Fig. 6, p. 341), and Ruge's [79] illustration (p. 313), coincide with our hydradenoma papilliferum. Hoeck's [46] tumor of the vulva called tubular hydradenoma probably belongs to our deep hydradenoma papilliferum, although the photograph seems less typical than the description. Blau [4] showed very good illustrations of the more solid type of hydradenoma papilliferum which he described as an adenoma consisting principally of tubules.

We believe that the majority of the tumors described as adenocarcinoma of the vulva [62] are benign and should be considered hydradenoma papilliferum.

There are two less common forms of hydradenoma papilliferum which may conveniently be termed (a) superficial and (b) intermediate. The superficial hydradenoma papilliferum is a tumor of the terminal ducts, primarily. There is dilatation of the ducts, but usually not to cystic proportions, and proliferation of the epithelium forming low papillary infoldings. Intraductal growths are sometimes seen but they are not an essential part of the picture. Perhaps the most striking change is in the character of the epithelium. The two layers of cells of the normal duct usually remain distinct. The lining cells become tall-columnar. The cytoplasm is commonly faintly basophilic and the nucleus lies in the center or at the base of the cell. The free border of the cell may be lipped or frayed. Near the orifice there is frequently a pseudostratification of cells and occasionally squamous metaplasia and keratinization. Alterations of the secretory part of the gland consisting of dilatation and varying degrees of hyperplasia seem to be secondary to the changes in the terminal ducts, but occasionally the epithelial proliferation in the secretory alveoli is marked.[54] A moderate fibroblastic proliferation and inflammatory reaction in the surrounding corium usually appear as an integral part of the process.

The gross characteristics are not distinctive. The tumor may be large or small, more or less papillomatous or polypoid, or form a plaque by confluence of small growths. It sometimes resembles a condyloma. It has been described as occurring chiefly on the face,[76] on the scalp [27] and in the region of the shoulder, axillae, or genito-inguinal folds.[38] A pore-like opening is often present from which serosanguinous fluid and papillary structures may be expressed and it is frequently crusted with hyperkeratotic scales or dried secretion.

The nature of the process has not been definitely proved. Some of the tumors have been described as congenital.[61] The association with other skin lesions as naevus unius lateris [28] and chronic eczema [76] and the inflammatory changes, has suggested a reactive process.[7]

We have seen only two typical examples of the superficial hydradenoma papilliferum (41-3362, 10316). A third tumor (37-2022) classified with the carcinomas may have been originally a superficial hydradenoma papilliferum. It was a congenital lesion in which malignancy became manifest in middle life. In the center of the tumor were enlarged ducts lined by proliferating epithelium with dilated and slightly hyperplastic secretory alveoli beneath. On each side of the tumor was typical basal cell carcinoma arising from the superficial epi-

thelium and from hair follicles. The carcinoma extended to a slight extent through the midcorium between the secretory and the ductal portions of the lesion. Fibrosis of the stroma was rather marked.

Reviews of the literature in 1936 [3] and in 1933 [76] give a total of 33 published cases of the superficial hydradenoma papilliferum. It has been commonly known as naevus syringocystadenomatosus papilliferus.[27, 31, 38, 76, 80] Elliott [28] described the tumor as adenocystoma intracanaliculare. Unna's [95] cylindrical-celled cancer (p. 711), which he described as arising from metaplasia of surface epithelium, may possibly conform to the superficial hydradenoma papilliferum. Werther's [102] syringadenoma papilliferum (naevus syringoadenomatosus papilliferus) has some of the characteristics of our superficial type of hydradenoma papilliferum but it seems to us to have more in common with the usual form of hydradenoma papilliferum.

The intermediate type of hydradenoma is a rare tumor which suggests a growth from a congenital abnormality. There are no distinctive clinical characteristics. It is a tubular, branching structure lying usually in the upper or middle corium. Epithelial proliferation is sluggish and there is relatively little tendency to stratification of cells, papillary infoldings, or solid growth. It is generally classed with the naevi syringoadenomatosi and considered congenital. McCarthy's [61] and Wolters' [107] description of naevus syringoadenomatosus and Eller's [27] sweat gland nevus show somewhat more proliferation than we have seen in the tumors in this group, but otherwise are similar.

The tumors we have classified as varieties of hydradenoma papilliferum have been described in the literature as distinct tumors. In thus grouping them we do not wish to imply any relationship other than a similarity of the type of growth. There are many differences. The superficial tumors are often associated with inflammation; both superficial and intermediate types have characteristics suggesting a congenital malformation, and the deep tumors are more complex neoplasms, probably acquired. Atypical forms are frequently described that do not fall clearly into any group. Many of these appear to be congenital.[10, 63]

3. *Hydradenoma*

Hydradenoma is a solid tumor of sweat gland. This is more common than all the other tumors of sweat glands together, and less frequently recognized as originating from these structures. It is a grossly discrete, solitary or multiple growth, sometimes appearing in groups, that is found chiefly, although not exclusively, on the face and scalp. It produces a low mound-like elevation, except on the scalp where it may be pedunculated. The tumor is frequently located in the subcutaneous tissue and lower corium but may involve the entire corium. Rarely it

seems to arise close to the epidermis. Ulceration is unusual. The tumor may be any size but is rarely more than 4 cm. in diameter. Growth is slowly progressive to a certain limit and thereafter the tumor usually remains of the same size.

In a few tumors, a partly papillary structure suggests development from a hydradenoma papilliferum, but the majority consist essentially of alveolar spaces embedded in compactly arranged, solid cell masses and strands. The alveoli, numerous or only occasional, have distinct cuboidal or columnar epithelium-lining cells with central or basal nuclei and are cuffed by more or less massive proliferation of smaller cells characterized by hyperchromatic nuclei and inconspicuous cytoplasm. The appearance of the alveolar cells and of the solidly massed cells is sometimes quite similar except for shape. Frequently, however, the alveolar cells stand out in sharp contrast, either because of deeply eosinophilic cytoplasm or because of abundant rather pale cytoplasm. The resemblance of these pale lining cells to normal secretory epithelium suggests origin from it, but these cells may also be seen in abnormal proliferation of the epithelium of the ducts (Figs. 4 and 5). We have not attempted to distinguish between hydradenoma of ducts and of alveoli because of the fact that under abnormal conditions the epithelium of these structures may have a similar appearance.

Although the alveoli are an essential part of the tumor, the diagnosis does not depend upon their presence but can be made on the architecture of the tumor and on the cell type. The distinct cell type that forms the solid masses may be described most clearly by comparison with the basal cell. It is rounded or polygonal rather than spindle in shape, and somewhat larger than the basal cell. The centrally placed nucleus is of medium size compared to the cytoplasm. There is considerable chromatin, but the nuclei are usually less dense than those of basal cells. Nucleoli are not prominent. The cytoplasm is quite variable in amount; it may be negligible or conspicuous. Some of the nuclei are naked, and, at the other extreme, the clear ballooned cytoplasm may suggest sebaceous epithelium,[41] except for its reticulated rather than foamy structure. Generally the cells have somewhat more cytoplasm than the basal cells and it is either faintly eosinophilic or basophilic, less commonly clear. The limiting membrane is sharp. Mitotic figures are not usually conspicuous. A few tumors show invasive growth and, rarely, anaplasia. Sutton [87] explained the hydradenoma, which he called syringocystadenoma nodularis, as a proliferation of sheath cells of the gland rather than as a proliferation of the secretory epithelium. This conjecture serves to emphasize the typical appearance.

In occasional tumors, this typical appearance is not seen and there

may be a close resemblance to basal cells or squamous cells. A few hydradenomas are continuous at one or more points with the epidermis and there is keratinization of the superficial part of the growth. Nevertheless, the manner of growth is usually more suggestive of metaplasia of duct epithelium than invasive growth of epidermis. Necrosis seems to be less common in relation to tumors of sweat glands than in other nonkeratinized epithelial tumors.

The architecture is a very helpful differential feature. The tumors lie in the mid- or lower corium and are not typically connected with any of the epithelial structures of the skin. The masses of cells are compactly arranged units in distinction from the loose, lobulated, or reticulated growth often seen in basal cell carcinomas. The alveoli are not to be confused with cystic spaces found in tumors of the hair matrix or basal cells as a result of degeneration of the stroma or of the tumor. They are less easily distinguished from the true alveoli of mucous gland tumors of the lip. The cells, though closely packed, are not uniformly aligned, and often have no clear orientation to one another. There is rarely any peripheral palisading as in tumors of basal cells or of the hair matrix.

In certain of the hydradenomas there is a characteristic tendency toward hyaline degeneration (Fig. 5). This appears to start as a hyaline or amyloid-like change either in the basement membrane, or as a fine ribbon weaving among the epithelial cells, and less commonly as a degenerative change within the cells. Finally, the major part of the tumor may be replaced by broad strands and masses of hyalin with squeezed epithelial cells in the interstices. This change has been described by Unna.[95] Although hyalin is found in the nonkeratinized tumors of basal cell or hair matrix origin, it is more clearly the result of degeneration of the tumor or stroma and the pattern of deposition is different.

There have been wide differences of opinion in respect to the nature of the hydradenomas. They have been considered as arising from hair follicles and sebaceous glands as well as from sweat glands [51, 78, 82, 98] and endothelium.[85] Location on the scalp has led to their inclusion with the ill-defined group of turban tumors. It must be acknowledged that in those hydradenomas without alveoli, origin from sweat glands cannot be proved. Furthermore, in some of the tumors, connection can be traced with the overlying epidermis or with hair follicles. The structure also has a certain resemblance to hair matrix carcinoma: narrow branching strands of cells, scattered whorls of nuclei about minute hyaline particles, and rarely, well formed hair follicles embedded in the tumor, not as an accidental inclusion but as an integral part of the growth.

Thirteen of our tumors were from both sweat glands and hair follicles. In one of these there was a suggestion of growth from sebaceous glands, but as basal cells rather than as differentiated sebaceous cells. Stromal proliferation is especially prominent in these tumors of both sweat glands and hair follicles.

The hydradenoma has been generally called cylindroma. There are several objections to this term. According to some usage, it carries a specific reference to hyalin. This is found in Ewing's [29] definition of cylindroma: "a tumor structure in which the stroma appears in the form of elongated, twisted, thickened cords of hyaline material." Certain tumors of salivary glands and nasal sinuses characterized by hyalin and cord-like arrangement of cells have been called cylindromas. A term so generally applicable leads to confusion of tumors of diverse origin.

Examples in the literature of our hydradenoma may be found in Krompecher's [55] illustrations (Figs. 6, 8 and 11) under the name cylindroma; in Watanabe's [98] description and plates of cylindroma; in Figure 5 of the sweat gland adenoma described by Weidman and Besancon; [99] and in Figures 20-A and 20-B of Geschickter and Koehler's [40] paper on epithelial tumors of the skin, and in many other papers on cylindroma and turban tumors.

4. Hydradenoid Carcinoma

Hydradenoid carcinoma is a carcinoma of sweat glands. Carcinoma of sweat glands has never been clearly defined in the literature and little care has been taken to differentiate it from other nonkeratinizing carcinomas on the one hand and from adenoma on the other. Moreover, the propriety of this classification of sweat gland tumors is questionable in view of the well known fact that they are not often clinically malignant. Malignancy has been attributed to each of the three types of benign tumor: syringoma, hydradenoma papilliferum, and hydradenoma. However, malignant degeneration of syringoma and the more differentiated types of hydradenoma papilliferum is probably very rare if it occurs at all. Certainly, some of those carcinomas described as arising from syringoma and hydradenoma papilliferum of the superficial type are more suggestive of coincident basal cell carcinoma.[76, 104] (as in our case 37-2022). Adenocarcinoma of sweat glands is described not infrequently, and usually as arising in hydradenoma papilliferum, notably of the vulva. In our opinion this diagnosis is seldom justifiable. The tumors are considered malignant on the basis of marked cellularity and absence of capsule and in most cases without any appreciable loss of differentiation. The tumors are easily shelled out and usually do not recur or metastasize. The thirty cases of "adenocarcinoma" of the

vulva recently published by McDonald [62] illustrate the problem. Ewing [29] mentioned adenocarcinoma of the sweat glands as a tumor which metastasizes late, but he did not give any criteria for distinguishing the adenocarcinoma from the adenoma. His illustrations entitled "tumor" and "adenocarcinoma" of sweat glands (Figs. 461 and 462, pages 906 and 907) correspond to our solid tumor or hydradenoma.

The commonest form of carcinoma is the solid carcinoma, and in most instances it results from malignant change of hydradenoma. Still, the differentiation of benign and malignant varieties of the hydradenoma has not been definitely established. Some observers consider all the solid tumors malignant. The uncertainty of diagnosis of the solid carcinomas is due in great part to theoretic consideration and to overemphasis of unusual tumors. It has been assumed that malignant tumors of sweat glands lose all their characteristic features on becoming malignant.[17, 95] Others have considered basal cell carcinoma or rodent ulcer as originating from any of the epithelial structures of the skin, sebaceous glands, hair follicles, and basal epithelium.[12, 19, 40, 55, 91, 97] Uchiki and Suzuki [93] spoke of a specific "medullary form" of basal cell carcinoma arising from the ducts. Unna [95] described a cylindrical cancer of sweat glands having a tubular structure with "widespread, central liquefaction." The cavity formation seems to have been a process of degeneration rather than of true alveolar formation. He suggested that the secretion of the cells might play a part in the degeneration. Dörffel [21-24] emphasized the basal cell origin of tumors of sweat glands and sebaceous glands, and cited a tumor of sweat gland that had sebaceous elements in the recurrence. Borrmann [5] illustrated a "corium carcinoma" spreading beneath the skin and growing out of ducts of sweat glands and hair follicles. Nonkeratinizing carcinomas originating from two or more cutaneous structures are seen occasionally and it is quite possible that undifferentiated carcinomas of sweat glands may not be distinguished from basal cell carcinomas. However, carcinomas with perfectly clear structure of sweat glands have been described and our concern is with these. A few of the carcinomas with a high degree of histologic malignancy have metastasized and recurred.

In considering the clinical aspects, one must take into account the great lack of interest and diligence shown by most writers with respect to adequate "follow-up" of patients having any type of cutaneous cancer. Unfortunately most of our own cases were not followed an adequate length of time.

Hufschmitt and Diss's [48] tumor recurred twice at short intervals. The recurrence of Woringer's [108] tumor took place after a 2-year interval. Eichenberg [26] reported an unusually interesting case of adenocarcinoma of the vulva with metastasis to inguinal lymph nodes. This was

believed to have developed from a hydradenoma papilliferum. There was marked proliferation with formation of solid masses and invasive growth. Other tumors that metastasized were reported by Moriconi [64] and Hedinger.[44]

We have listed in Table I tumors described as carcinoma of sweat gland. We have not included all of the cases in the literature. Some were too vague or too unusual and others were not clearly tumors of sweat glands.[34, 83, 84] These tabulated cases should not be considered as representative of carcinomas of sweat glands, as usually they have been reported because of features of peculiar interest. Pelagatti's [70] case, for example, suggests a basal cell carcinoma. Thierfelder [90] reported a tumor as spiradenoma which had nevertheless extended through the skull to meninges. Cornil's [15] tumor was not accepted by Unna,[95] who considered it identical with his cylindrical type of cutaneous cancer, which we interpret as carcinoma of basal cells or of hair matrix. Fordyce's[35] tumor, described as adenocarcinoma, corresponds to our hydradenoma. In this tumor the alveoli were more numerous than is often the case and it was considered malignant on the basis of "invasive growth." Ruge's [79] case is interesting chiefly because of the amount of attention it has received in the literature. The tumor was essentially hydradenoma papilliferum, encapsulated except for a few places without basement membrane. Ruge, himself, was conservative, admitting that the case was not absolutely clear, but inclined toward the view of a low-grade carcinoma arising from an adenoma. Landsteiner [56] did not accept Ruge's case but Schiffmann [81] did and reported a similarly doubtful tumor.

Several of the tumors present difficulties of interpretation,[9, 42, 66, 68] because of atypical characteristics such as pearl formation.[18, 81, 90] The high incidence of metastasis and recurrence among those tabulated is undoubtedly due to selection of the cases.

The long history in many cases suggests that the tumors arise from adenomas.[36, 57] Christot [13] reported a carcinoma interpreted as arising from sweat glands that had been present but quiescent since infancy but which had grown rapidly during the year and a half before removal and weighed 450 gm. He traced the development of the tumor from hypertrophy of the sweat glands through hyperplasia to epithelioma. The cancer of sweat gland described by Cornil [15] has some similar points. A papillary tumor on the leg of a man, 59 years old, had been present since birth but had lately ulcerated. The author described hypertrophy of sweat glands and metamorphosis of the epithelium into the pavement type with large fat droplets.

In Table II are listed our tumors of sweat glands. Only six of our tumors were frankly malignant from the point of view of invasive

TABLE I

Reported Cases of Sweat Gland Carcinoma

Author	Date	Patient		Location	Size and appearance	Duration and symptoms	Treatment and results
		Age	Sex				
Cornil[15]	1865	59	M	Leg	2 cm.; irregular	Entire life; ulcerated 6 months	Excised; no recurrence
Christot[13]	1866	33	F	Back	Child's head; ulcerated	Since childhood; recent ulceration	
Thierfelder[90]	1870	50	F	Forehead at hair margin	Hen's egg	4 yrs.; invaded frontal bone to meninges	Operation; death from meningitis
Morisani[65]	1887	30	F	Fifth toenail		5 yrs.; invaded tarsal bones	Excised; recurred once; died after 4 mos.
Darier[17]	1889	71	M	Chin		2 mos.	
Wierzbowski[105]	1892			Rt. anterior thigh	Goose egg		
Fordyce[35]	1895	35	M	Leg	Ulcerated, firm; one-half of small egg		Excised
Campanini[9]	1897	50	F	Forehead	Ulcerated; occurred in scar	5 yrs.	
Antonelli[1]	1902	43	F	Rt. labium majus	Multiple nodules	6 mos.	No metastasis
Deichstetter[18]	1902	65	M	Lt. elbow laterally	8 x 11 cm.; ulcerated	½ yr.	
Lusena[59]	1904	63	M	Gluteal region		Few mos.	
Ruge[79]	1905		F	Posterior commissure of vulva	0.7 x 1.1 cm.		
Wolfheim[106]	1907		F	Cheek	Linseed		
Hedinger[44]	1911	48	F	Scalp	4 x 5 cm.; grayish red, ulcerated	Since childhood; growth 10 yrs.	Excision of tumor and two lymph nodes, each 1 cm., with metastases
Ricker and Schwalb[77]	1914	45	F	Rt. upper eyelid	1.2 x 1.2 cm.	6 yrs.	

TABLE I—(*Continued*)

Author	Date	Patient		Location	Size and appearance	Duration and symptoms	Treatment and results
		Age	Sex				
Schiffmann[81]	1920		F	Labium majus	Bean; reddish	2½ mos.	Excision
Ohno[66]	1924	70	M	Scalp	3 x 3 cm.; eroded, red, hard margins, ulcerated	10 yrs.	
Calissano[8]	1926	63	M	Inguinal region	Hazelnut; reddish		
Diss and Peterschmidt[19]	1926	67	M	Rt. lower eyelid	1 x 1.5 cm.; ulcerated, hard	2 yrs.	Excised; recurred once
Grynfeltt[43]	1929	26	F	Lt. inguinal region	Linseed	5 yrs.	
Kehrer and von Jaschke[53]	1929	40	F	Lt. labium majus	Pea; had an opening externally	6 yrs.	
Hufschmitt and Diss[48]	1929	61	F	Scalp	Large; ulcerated, firm, violaceous	37 yrs.	Excised; recurred in 6 mos. with adhesion to skull and periosteum; regional metastases
Moriconi[64]	1931	59	M	Axilla	Walnut	6 mos.	Radical axillary dissection; metastases in regional nodes; well 5 yrs. later
Orol Arias[68]	1933		F	Rt. heel	Ulcerated	3 yrs.	
Eichenberg[26]	1934	30	F	Labium majus	0.5 cm.		Excision left labium and left inguinal lymph nodes with metastasis; well 2 years later
Gougerot, Albeaux-Fernet and Dreyfus[42]	1934	43	F	Rt. leg	Hazelnut, hard, 25 cm.	3 mos.	Excised; died; no autopsy
Pelagatti[70]	1934	62	M	Lt. upper lip	Hazelnut	4 mos.	Excision
Loos[57]	1936	68	M	Heel	Hen's egg		
Fessler[32]	1939	55	F	Abdominal skin	6 cm.; reddish	Over 1 mo. (indefinite)	Excised

TABLE II

Tumors of Sweat Glands

Number	Age	Sex	Location	Size	Duration	Rate of growth	Remarks
				Syringoma			
36–279 T. C. 272	26	M	Scalp	2 cm.	3 mos.		Syringoma but with atypical clinical and histologic features
				Hydradenoma Papilliferum			
S–28–154	60	F	Back		Congenital		Hydradenoma papilliferum, discrete, partly solid growth, keratinized masses suggesting keratinization of ducts, upper corium
28–1805	38	M	Scalp		18 mos.		Hydradenoma papilliferum, discrete, solid as well as papillary growth, lower corium
29–2934	49	M	Head				Hydradenoma papilliferum, discrete, simple structure, lower corium
31–1968	40	F	Abdomen				Hydradenoma papilliferum, discrete, cystic and solid, much degeneration of tumor, lower corium
35–974	65	F	Scalp	2 x 1.5 x 0.4 cm.	Many yrs.		Hydradenoma papilliferum, complex papillary structure, both glands and ducts appearing to be involved, upper corium
38–996	45	F	Lt. infrainguinal region	Egg	3 yrs.		Hydradenoma papilliferum, discrete, lower corium
42–1293	54	F	Finger	3 cm.	6 mos.		Hydradenoma papilliferum, cyst with low papillary growth at periphery, in part suggesting apocrine gland, lower corium
42–2430	53	M	Neck	2 cm.	Congenital	Slow, past 10 yrs.	Hydradenoma papilliferum, some solid growth, some suggestion of apocrine gland, subcutaneous tissue
46296				2 cm.			Hydradenoma papilliferum, cyst without lining but with typical papillary structure lying free in center, subcutaneous
1280		F	Labium				Hydradenoma papilliferum, discrete, complex structure, lower corium
15707	40	F	Face				Hydradenoma papilliferum, encapsulated, intracanalicular growth, partly papillary but chiefly solid, some mucinous change in stroma, lower corium
				Hydradenoma Papilliferum Superficial			
41–3362 10316	31	F	Forehead	2 x 2 x 3 cm.			Hydradenoma papilliferum, superficial Hydradenoma papilliferum, superficial

41–3362 10316	31	F	Forehead	2 x 2 x 3 cm.			Hydradenoma papilliferum, superficial Hydradenoma papilliferum, superficial

Hydradenoma Papilliferum Intermediate

18–179	58	M	Lower lip		Several yrs.		Hydradenoma papilliferum, intermediate
42–413 T. C. 525	35	F	Near nose left cheek				Hydradenoma papilliferum, intermediate

Hydradenoma

23–1570	52	F	Forehead	2 cm.	8 yrs.		Secretory(?) type
25–1666	74	F	Scalp	Hen's egg	6½ yrs.		Secretory(?) type
33–1879	40	M	Rt. supra-orbital	3 x 1.5 x 0.8 cm.	3 mos.		Secretory(?) type
38–3223	58	M	Knee	3 x 5 cm.	10 yrs.		Secretory(?) type
39–1518	20	M	Leg	2 x 2 cm.	2 yrs.		Secretory(?) type
39–3141	46	M	Shoulder	Small pea	2 yrs.		Secretory(?) type
40–1278	63	F	Rt. side of face	3 cm.	10 yrs.		Secretory(?) type
41–4430			Scalp				Secretory(?) type
17–2		M	Forehead	2 x 1.5 x 1 cm.			Duct(?) type, hyalin in tumor cells
25–1982	40	F	Forearm	Large walnut	Since childhood		Duct(?) type, hyalin
27–1113	33	F	Forehead		2 ± mos.		Duct(?) type, suggests an originally papillary growth
27–1419	23	M	Rt. thigh				Duct(?) type
S–28–505	33	F	Finger	2 x 0.5 x 0.5 cm.	4 + yrs.		Duct(?) type, pedunculated
28–1910	55	F	Chest above breast	Pea	6 mos.		Duct(?) type
29–3067	31	F	Leg	Pea	10 mos.	Rapid	Duct(?) type, very cellular, few glands, much degeneration in stroma
30–397	24	M	Ear				Duct(?) type
30–1416	57	F	Lip				Duct(?) type
32–188	50–60	M	Back of head		2 mos.		Duct(?) type
T. C. 173							
32–2401	60	M	Forehead	25 cent piece	5 yrs.		Duct(?) type, hyalin
33–S–468	53	F	Over rt. eye	5 cm.	5 yrs.	Slow	Duct(?) type, died 4 yrs. later, carcinoma of ovary with metastases
			Lt. hip	5 cm.			
33–S–822	34	M	Rt. temporal region	3 x 2 cm. raised 5 cm.			Duct(?) type, last seen 9 yrs. later, also separate basal cell carcinoma
35–697	66	F	Scalp	1 x 2 cm.	15 ± yrs.	Activity past 6 mos.	Duct(?) type
35–908	36	F	Rt. cheek	Pea	2 yrs.		Duct(?) type
35–1377	43	F	Forehead above eyebrow		16 mos.		Duct(?) type

TABLE II—(*Continued*)
Tumors of Sweat Glands

Number	Age	Sex	Location	Size	Duration	Rate of growth	Remarks
				Hydradenoma (continued)			
36–S–565	67	F	Front of rt. ear	1.5 cm.	14 yrs.	Slow	Duct(?) type
36–996	83	F	Rt. ear	1 cm.	5–6 yrs.		Duct(?) type, entire corium
36–2541	68	F	Hand	Bean	10 yrs.		Duct(?) type
37–S–349	91	M	Rt. cheek	2 cm.	Pimple sev. yrs.	Increase size past 6 mos.	Duct(?) type
37–1781	67	F	Temporal region		5–6 yrs.		Duct(?) type
37–2332	45	F	Thigh	Pea	20 yrs.		Duct(?) type, some hyalin
39–1394	78	F	Below xiphoid		15 yrs.		Duct(?) type
39–1413	48	M	Upper arm		Few yrs.		Duct(?) type
40–438		F			11 yrs.		Duct(?) type
40–1003 T. C. 440	51	F	Forearm	6 x 4 mm.			Duct(?) type
41–485	35	F	Rt. temple				Duct(?) type
41–3856	45	F	Scalp	2 x 1.5 cm.	3 mos.		Duct(?) type, entire corium, much hyalin; in part suggests keratinization where ducts approach epidermis
42–829	43	F	Ext. auditory canal at orifice	2 cm.	10 yrs.		Duct(?) type, entire corium, early hyalin
42–981	25	M	Below ear	1″ diam.	2 yrs.		Duct(?) type
42–1529	72		Rt. lower eyelid				Duct(?) type
42–1555	65	F	Forehead	⅜ x ¼ x ⅛″	20 yrs.		Duct(?) type, whole corium
78	45	F	Rt. thigh	2 ± cm. diam.	20 yrs.		Duct(?) type
13680	50	F	Arm				Duct(?) type
35590	47	F	Neck	2 cm.			Duct(?) type, early hyalin
44499	70	F	Face				Duct(?) type, midcorium
45276a	64	M	Scalp	16.5 cm.	40 yrs.		Duct(?) type
45276b	64	M	Back	5 cm.			Duct(?) type
46911	51	F	Arm	2 cm.			Duct(?) type
				Hydradenoma with Associated Hair Follicle Tumor			
30–1513	73	F	Scalp				
30–2489	59	F	Lip				Many cysts, fibrosis with calcification, subcutaneous
31–1789	35	F	Thigh	1.5 cm.	8–10 yrs.		Fibrosis of stroma with much fat
32–1275	56	M	Nose	10 cent piece	4(?) yrs.		Much fibrosis and fat in stroma
33–2494	31	M	Upper lip	1 cm.	2 yrs.		
34–1415	60	F	Sacroiliac region	2½ x 2½″	16 yrs.		Chiefly duct type with some foci of tumor of hair follicle

33–2494	31	M	Upper lip	1 cm.	2 yrs.		
34–1415	60	F	Sacroiliac region	2½ x 2½"	16 yrs.		Chiefly duct type with some foci of tumor of hair follicle

Hydradenoma with Associated Hair Follicle Tumor (continued)

35–1181	50	F	Rt. breast	Less than 25 cent piece	2+ yrs.		Growth apparently originating from sebaceous glands, hair and coil, some foci of keratinized cells; negative
37–2022	43	F	Rt. temporal	50 cent piece	20 yrs.		Hydradenoma papilliferum with basal cell carcinoma and hair matrix carcinoma, congenital
39–S–529	77	F	Abdomen	3 cm.	15 yrs.		Much fat in the stroma
42–1205	38	M	Upper lip	½ cm.	Few yrs.		Some cysts, marked mucinous change in stroma
15605	55	M	Scalp vertex	2.0 cm.			

Hydradenoma Arising from Apocrine Gland

26–1276	30	F	Labium				
29–1556		F	Vulva				
37–943		F	Urethra	3–4 mm.	1 yr.		
39–1461	55	F	Below ear lobe	0.5 cm.			
40–3609	45	F	Labium				
13343	55	F	Labium rt.				
30211	61	F	Labium, rt.	3–5 mm. diam.			
37056	60	F	Near anus	0.8 cm.			

Mixed Tumors

C. S. 15–116			Nose				
36–2339	67	M	Temporal region	Pea	1 yr.		
37–838	60	F	Upper eyelid	2 x 1 x 1 cm.	About 1 yr.		
37–2222	62	M	Scalp	1.5 cm.	Long		
W635	38	M	Rt. hand	3.5 cm.			

Hydradenoid Carcinoma

32–627 T. C. 183	73	F	Ear				Adenocarcinoma invading cartilage
37–1814	81	M	Face	1.5 x 1 x 0.5 cm.	2 mos.		Adenocarcinoma with metaplasia suggesting basal cell carcinoma with foci of keratinization
37–2023	76	F	Angle of scapula	Hen's egg	Congenital	Rapid past 6 weeks	Invasive growth from hydradenoma papilliferum, anaplastic part solid, much necrosis
39–809	80	F	Thigh	6 cm.	30 yrs.		Hydradenoid carcinoma, parts of which resemble basal cell carcinoma, suggestion of origin from surface
39–1475	65	F	Thigh	Marble	2 mos.		Hydradenoid carcinoma arising from hydradenoma papilliferum
40–2059 T. C. 454	62	F	Anus	11 cm.			Hydradenoid carcinoma arising from hydradenoma papilliferum of apocrine glands with foci of hair matrix carcinoma; carcinoma *in situ*

growth. A single recurrence was observed in four cases and there was no instance of metastasis. All of these tumors were excised.

One of our tumors (40-2059) deserves special mention. It was a cauliflower plaque completely surrounding the anus and measuring 11 cm. in greatest diameter. The growth did not extend into the canal. The epidermis covering the papillary growth was greatly thickened by active proliferation of cells which in part was atypical and represented carcinoma *in situ*. There was also invasive growth from the epidermis. Filling the corium was a tumor of sweat glands and of hair follicles, in part anaplastic. The tall acidophilic domed cells of the glandular portion suggested origin from apocrine gland. The malignant change in the epidermis and in the cutaneous appendages appeared to be independent.

Summary

Tumors of the sweat glands are probably fairly common but they are rarely seen in the laboratory, as they are seldom removed except in those cases where they are unusually large, as they tend to be on the scalp; or where they are annoying because of their location, as on the vulva.

They tend to occur on certain parts of the body, such as the scalp, anterior chest, axillary folds, gluteal and perineal regions, and labia.

A congenital origin has been assumed by most writers in spite of the fact that with the exception of syringoma, which typically occurs at puberty, the majority of these tumors are noted first in adult life. The chief support of this view is the organoid histologic structure and the fact that some of them arise from several skin components.

There are two main histologic types, papillary and solid. The latter is more common. The solid forms may resemble basal cell carcinoma, but the pattern of growth is quite different and the alveoli lined by cuboidal epithelium embedded in solid cell masses make the origin clear. The origin of basal cell carcinomas from the sweat glands is unlikely on theoretic grounds and has yet to be proved. Differentiation of tumors arising from ductal portions of sweat glands as contrasted to alveolar is uncertain.

Carcinomas of sweat glands have been described on the basis of histologic invasive and anaplastic growth, but metastasis is exceptional. While there are rigid diagnostic criteria for hydradenoma and hydradenoid carcinoma, the failure to apply these uniformly has led to much confusion in the differential diagnosis.

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C. Tumors of Specialized Sweat Glands

Tumors of specialized sweat glands, ciliary, apocrine, and ceruminous, are of theoretical interest, but so far as we know their histologic differentiation has no clinical importance.

1. Ciliary Glands

The ciliary gland or Moll's gland is a specialized sweat gland on the lids in close relation to the eyelashes. It differs in having a simpler coil structure and wider lumen and in opening near or into the hair follicle. According to Huber and Picena [4] an additional means of differentiation is an apocrine-like appearance of some of the cells of Moll's glands. Sweat glands of the ordinary sort are also found on the eyelid. We have no first-hand knowledge of tumors arising from Moll's gland but a few tumors have been reported. Two useful reviews are by Huber and Picena in 1932 and by Hagedoorn [3] in 1936. The earliest reported cases were those of Salzmann [7] and Wintersteiner.[8]

Few authors are willing to assert definitely that the tumors are of Moll's glands rather than of the ordinary sweat gland. Letulle and Duclos [5] wrote with a certain amount of confidence in their case, on the basis of absence of acinus formation, and the prominent myofibrils and elastic fibers around the tubular structure of the tumor. Coats [1] felt that the absence of hairs in his tumor, an adenocarcinoma, would probably indicate that it was not from Moll's gland. Zeeman's [9] tumor, which appeared after the removal of a cyst from the eyelid, is not alto-

gether convincing; it resembles rather a basal cell carcinoma. Nichelatti [6] and Huber and Picena [4] described cystic adenomas. These tumors occur in adults and grow slowly. The rapidly growing tumor reported by Gault and Legait [2] seems to be exceptional in this respect. Recent rapid growth or, rarely, ulceration was the usual reason for operation.

All of the tumors have been considered as adenomas except that of Coats,[1] which he called adenocarcinoma on the basis of histologic invasive growth. Recurrences after surgical removal have not been reported.

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2. Tumors of Apocrine Glands

The apocrine glands occur principally in the axilla, the nipple, the genital and anal regions, and along the course of the embryonic milk line, but they may be found occasionally in almost any part of the skin. Some writers have classed them with the sex glands because of the fact that they develop at puberty and have been described as changing in size with the menstrual cycle. The secretory process is similar to that of milk. The general architecture resembles that of dilated sweat glands, but the epithelium is quite different. The cells are two to three times as large, and are tall cuboidal or columnar with a prominent, domed, free border. The cytoplasm is eosinophilic and frequently contains small fat droplets and pigment granules which react positively for iron.[6] The myoepithelial cells are large. The lumen of the secreting portion is several times larger than that of the sweat gland.[13]

The general impression of the rarity of these tumors is probably due to the fact that they have been reported with tumors of the ordinary

sweat glands. Many of the hydradenomas of the vulva arise in apocrine glands. A few writers have attempted to demonstrate the origin of syringoma and epithelioma adenoides cysticum from apocrine glands.[3, 7, 8, 12] Ewing [5] does not discuss tumors of apocrine glands as such, but includes an illustration (Fig. 249) with the caption "Adenoma of axillary sweat glands. An occasional source of mammary carcinoma."

A clinically malignant carcinoma of the apocrine gland has not been reported so far as we know.* McDonald [11] recently reported twelve adenocarcinomas of the apocrine gland from the vulva. These differ from adenomas only in the mitotic activity and the microscopic invasive growth. It has been suggested that extramammary Paget's disease may in some instances be due to invasion of epidermis by tumor cells from an underlying carcinoma of apocrine gland but clear proof is lacking.[2, 4, 9, 14] Creighton [1] associated "chimney-sweep's" cancer with the apocrine glands of the scrotum.

In our series of 121 tumors of cutaneous glands there are 9 from apocrine glands: 6 from the vulva, 2 from the anus and 1 from below the ear, a quite characteristic distribution. The tumors lie deep in the corium and are 1 to 2 cm. in diameter. The cells usually are typical throughout. Occasionally small foci of apocrine cells are seen in a tumor otherwise of the ordinary sweat gland type. The height of the cells varies considerably, but as a rule ranges from one and one-half to three times the width. The cytoplasm is homogeneous, moderately dense, sharply defined, and is intensely acidophilic. The cells at times contain a few fine vacuoles and a small amount of brownish to golden-yellow, finely divided, nonrefractile pigment, positive for iron, midway between the nucleus and the free edge. The nucleus, often round, may be ovoid and commonly lies about one-third of the distance from the basement membrane to the lumen. It is moderately rich in chromatin with a nucleolus of average mass.

The papillary cystadenomas have either a simple or complex structure. The vascularization is ordinarily poor, but there is virtually no evidence of hemorrhage or of degeneration. Other than in papillary projections, the tumor carries little or no stroma, merely expanding that portion of the corium in which it occurs. The contents of the cyst into which the papillary projections extend are usually clear without evidence of mucin, or degenerative products. Two of our tumors are solid adenomas and the others papillary, having the structure of hydradenoma. Two tumors, one solid and one papillary, have histologic malignant properties, active mitosis and invasive growth. Of particular

* The so-called sweat gland carcinoma of the breast [10] will be described separately.

interest was a carcinoma *in situ* in the epidermis overlying the solid tumor. We are in doubt as to the propriety of considering any of the tumors of apocrine glands as carcinoma in view of their apparently invariable benignity.

Summary. Tumors of apocrine glands are not uncommon and occur chiefly on the vulva and near the anus. There is no clear proof that they are clinically malignant.

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3. Tumors of Ceruminous Glands

The ceruminous gland is individualized by a refractile pigmented secretion. In other respects it resembles the apocrine gland with all the characteristic features exaggerated: the glands are larger as are also the secreting cells with their domed free border; lipoid and pigment (iron-containing) are especially conspicuous and the myoepithelium is more prominent.

A very few tumors of these glands have been described. Brock [2] and Sprenger and Prietzel [9] have reported adenomas of the secreting portion and Alonso,[1] in a general work on tumors of the ear, cited other cases. Carcinoma of the ceruminous gland would seem to be an extraordinarily

rare tumor. There are only two unequivocal cases in the literature: one case reported by Montpellier and Laffargue [5] and that of Warren and Gates.[10] Two others which may fall in this group are those of Sprague [8] and of Yearsley and Butterfield.[11] Carcinomas of the ear canal, whose histology was not clearly specified, have been reported by Furstenberg,[3] Richter,[6] Schall [7] and Lukens.[4]

We have one tumor of ceruminous gland, a carcinoma.[10] It is of particular interest because of the gradations of proliferative change, from hyperplasia to highly malignant invasive carcinoma involving lymphatics, nerves and parotid gland. Even in the least differentiated portions there are some of the characteristics of the normal structure: excessive lipoid giving the cytoplasm a ballooned, reticulated appearance, and abundant pigment in powdery granules or in large aggregates, sometimes extruded from the cell.

The tumor presented as an ulcerated lesion in the groove behind the ear lobe rather than in the auditory canal. This superficial ulcerated portion of the tumor was the least differentiated; the less malignant portions and the glandular hyperplasia were near the normal ceruminous glands of the canal. The tumor had been noticed a year before it was removed and latterly had grown rapidly and resulted in facial paralysis. It measured 3 cm. in diameter and grossly was partly scirrhous and partly cystic. Although microscopically there was extensive lymphatic invasion, no gross metastases had made their appearance up to 6 months after removal.

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D. Tumors Ascribed to Sweat Glands

1. So-Called Sweat Gland Carcinoma of the Breast

Since the term "sweat gland carcinoma" has been used to describe certain tumors of the breast, this group of carcinomas must be considered in a discussion of the tumors of sweat glands. "Sweat gland carcinoma" of the breast is said to be differentiated from carcinomas of mammary glands by the following features: location near the skin and hence a tendency to early ulceration and pain; a yellow color; and a histologic structure of columnar cells with acidophilic, opaque, somewhat granular, and sometimes fatty cytoplasm reminiscent of apocrine glands.[7] For this last crucial feature to carry any weight one or more of the following assumptions is necessary: First, that sweat glands exist below the corium in mammary tissue. If this be true, the condition is very rare and is not found in the breast tissues seen in our laboratory. Second, that the resemblance of the cells of these mammary tumors—pale, acidophilic, and columnar—to those of apocrine glands implies origin from sweat glands. In pathologic conditions such as chronic cystic mastitis, such cells are frequently seen in ducts or acini continuous with readily recognizable mammary epithelium. Third, that breast glands are intimately related to sweat glands embryologically, and a reversion to the latter may occur. All of the skin appendages, as well as the mammary gland, derive from primitive surface epithelium independently. A more complete discussion may be found in Ewing.[5] While the resemblance of the cells of some breast carcinomas to apocrine cells has long been recognized, the histogenetic relationship has not been established.

Cahen [1] first interpreted the cysts of the breast lined with eosinophilic, distinctly lipped cells as sweat gland retention cysts. Creighton [2] explained these eosinophilic cells as an anomalous reversion to the sweat gland type of epithelium. Delbet and Mendaro [4] described this epithelium as "idrosadenoid." Herzenberg [6] found in apparently pathologic breasts of a stillborn infant multiple cysts lined by eosinophilic epithelium which he believed were dilated apocrine glands. Von Saar [9] thought such structures represented arrested differentiation of mammary tissue and Prym [8] spoke of dedifferentiation or metaplasia to an embryologically earlier type of lacteal duct. Dawson [3] suggested that they represent a "past proliferative phase."

Conclusion. We do not recognize the so-called sweat gland carcinoma of the breast as being a true tumor of sweat glands but rather as a tumor of mammary epithelium.

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2. Turban Tumors

The so-called "turban tumors" of the scalp are benign, multiple, largely confined to the scalp, and of slow growth. They typically appear at puberty or in early adulthood, especially on females, and are familial. Ancell [2] reported a case in which tumors appeared in 4 generations of a single family. The epithelial pattern is variable depending on the structure from which the tumor originates. The rare sarcomas of the scalp [3, 12, 27, 33, 35, 48] should not be included in this group.

In the early literature [23, 31, 45] these tumors were referred to as endotheliomas, as were most of the nonkeratinizing epitheliomas of the skin before Krompecher's [28] definitive work. Ewing [18] discussed the endothelial versus epithelial characteristics of the tumors. The term "nevoid" has been considered suitable inasmuch as it indicates the embryonic or congenital nature of the tumors which both the clinical manifestations and organoid histologic structure suggest.[8, 14, 24, 29, 40, 46, 51, 53] Macleod [30] and Binkley [8] considered that these tumors arise from embryonal rests and are relatively undifferentiated ectodermal structures which may resemble hair follicles or glands. Ewing pointed out the histologic resemblance of turban tumors to cylindromatous tumors of salivary and lacrimal glands and mucous glands of the nasal septum, accessory sinuses, and other locations. All of these tumors are composed of small hyperchromatic cells which tend to have an organoid

arrangement. But the point of particular interest which they have in common is the characteristic hyaline and sometimes myxomatous alteration, as well as the fibroblastic proliferation of the surrounding stroma. Opinion has been fairly evenly divided among writers as to whether the tumors are sebaceous,[5, 10, 38, 39] derived from coil glands,[4, 11, 26, 37, 47] or from hair follicles.[6, 8, 34, 42, 44, 49, 50, 51] The fact that they are generally considered to be of the basal cell type seems most important.[1, 6, 8, 9, 14, 17, 18, 19, 21, 25, 28, 29, 30, 32, 36, 40, 41, 44, 46, 49, 52, 53]

Some of the terms which have been applied to multiple tumors of the scalp in the past are as follows: benign cystic epithelioma of the scalp; [15] benign multiple epithelioma of the scalp; [16] familial cylindroma; [43] sebaceous tumors of the scalp; [38] primitive sebaceous epitheliomas; [5] cylindroma; [7] trichadenoma cylindromatosum; [11] naevus epitheliomato-cylindromatosus; [8] carcinoma basocellulare hyalinicum; [28] hyaline-like sweat gland epithelioma; [37] multiple sudoriparous adenoma; [4] syringoma of the scalp; [19] sweat gland carcinoma; [26] benign multiple basal cell epithelioma; [1] congenital endotheliomata; [27] multiple endotheliomas of the scalp; [31] endothelioma of the skin and turban tumors; [45] multiple sarcoma; [12] withering sarcoma; [3] confluent tumors of the scalp; [35] naevoepithelioma adenoides.[24] In spite of this diversity it seems clear that most authors agree on certain main points:

1. The tumors are multiple, benign, or, at most, of histologic malignancy only.

2. The histologic features are variable within the limits of basal cells or the cells of cutaneous appendages.

3. The cells are nonkeratinized, with few exceptions.

4. Cysts, hyalinization of stroma, and frequently cylindromatous arrangement occur.

5. Ulceration or fixation is rare.

The frequency of these tumors in relation to other epithelial tumors of the skin cannot be determined with certainty, partly because of the lack of uniformity in the interpretations of different observers. Ronchese [39] accepted 31 cases from a total of 50 reported in the literature. This seems far too low an incidence.

Patients do not come for treatment until the tumors cause inconvenience, which, because of their very slow growth, is a matter of many years. In the reported cases, the average duration of the tumors before treatment was 25 years and the average age of the patients at this time was 53 years.

The first lesions appear most frequently at the hairline of the temple and forehead as smooth, firm, nontender nodules with no discoloration of the normal, overlying skin. They are freely movable beneath the

skin and in the deeper structures. As time goes on, other nodules appear. These apparently develop as multiple, discrete foci rather than by infiltration from the primary nodule. The tumors often cover the entire scalp and may extend later around the eyes, ears, neck and upper part of the chest. Those on the nonhirsute parts of the skin are usually smaller and fewer in number.

One of our tumors of coil gland (45276) was entirely typical of the so-called turban tumor. The tumor had first been noticed on the front of the scalp in early manhood and had continued to grow slowly. Occasional trauma had caused bleeding and infection from time to time. After 40 years, the tumor presented as a lobulated mass covering the anterior half of the scalp and encroaching on the forehead and laterally behind the ears. The lobules were 3 to 5 cm. in height. Another elevated lesion, 2 cm. in diameter, was present on the back. Both had similar microscopic structure. Similar lesions were described in 4 generations of the family—the great-grandfather, mother, sister, and son. But none of 5 grandchildren was affected.

Excision is the usual method of treatment,[21, 22, 36] but because the tumors are so easily enucleated, the margin of excision is often not wide enough. There may be recurrence. Schuermann and Weber [44] advised supplementary radium therapy in some cases. Binkley [8] used interstitial radium in one case. Binkley,[8] Eller,[17] Delaye, Hugonot and Lacassagne,[14] and others have reported x-rays as ineffective. Because of the fact that tumors are usually numerous, Delaye, Hugonot and Lacassagne advocated galvanocautery. There has been no reported instance of malignancy developing in a turban tumor. Binkley [8] and de Beurmann [13] have reported spontaneous regression.

Summary. The turban tumor is not a special histologic entity and may resemble various slowly growing epithelial tumors of the skin and its appendages. It has been generally recognized that the clinical and histologic characteristics are those of a benign organoid tumor.

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3. Mixed Tumors of the Skin

The few reports of cutaneous mixed tumors in the literature have been reviewed recently by Scharla [4] and Simard.[5] The tumors have been reported from the hand, finger, lower leg, thigh, scalp, and flexor surface of the elbow. The diagnosis is not always simple. The typical basal cell carcinoma and some of the tumors of skin appendages frequently have very marked hyaline and myxomatous changes which may simulate cartilage and osteoid. The problem is well illustrated in the report by Geschickter and Koehler [2] who described certain cutaneous mixed tumors believed to originate in aberrant salivary gland. From the description and photographs it would be difficult to differentiate them from basal cell carcinomas with cystic and hyaline stromal changes. Simard considered his case a mixed tumor of sweat gland.

We have had five tumors of the skin in which cartilage or osteoid tissue and bone, or all three, made up an important part of the tumor. One grew on the hand and four came from the head. In all of the tumors the neoplasm developed in part from the coil glands; in three, hair follicles were involved as well and in one there was proliferation of sebaceous glands. Fibroblastic proliferation of the stroma with mucinous and hyaline change was prominent in all of the tumors.

As in the case of the tumors of salivary gland, it is an open question whether cutaneous mixed tumors are true teratomas or slowly growing epithelial tumors in which metaplasia of epithelium and/or stroma occurs.[1, 3]

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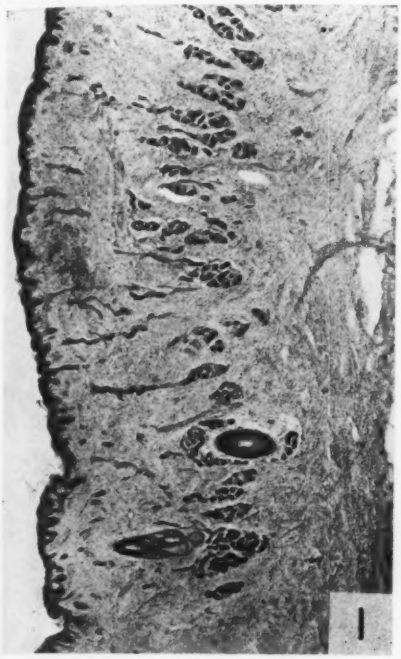
DESCRIPTION OF PLATES

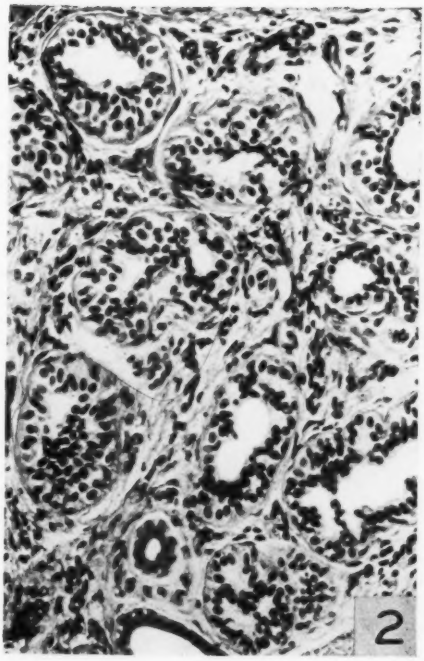
Plate 70

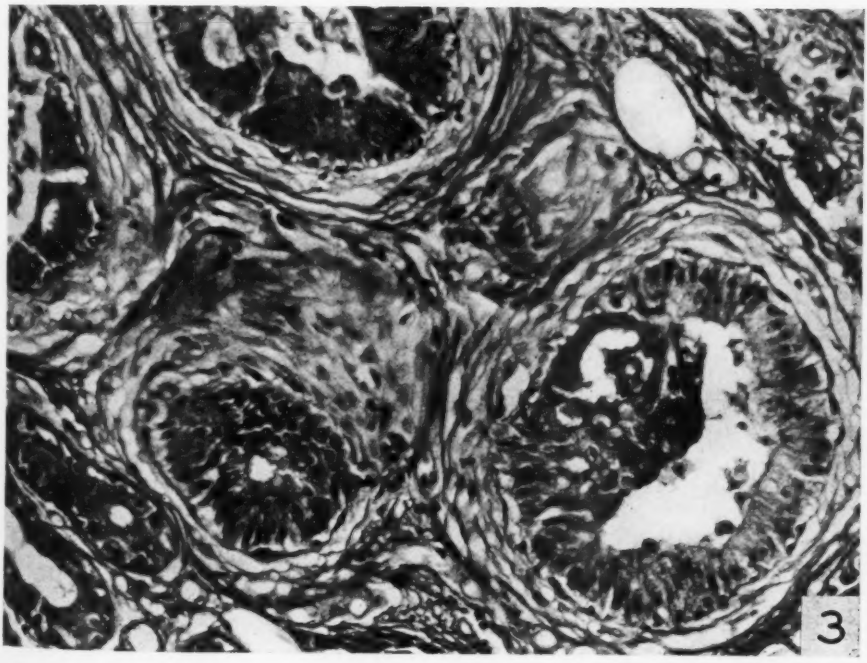
Fig. 1. Hyperplasia of ducts of sweat glands. Congenital lesion. Hematoxylin and eosin stain. × 15.

Fig. 2. Hyperplasia of secretory alveoli of sweat gland accompanying an inflammatory lesion. Hematoxylin and eosin stain. × 225.

Fig. 3. Metaplasia of secretory alveoli. Hematoxylin and eosin stain. × 375.







Gates, Warren and Warvi Tumors of Sweat Glands

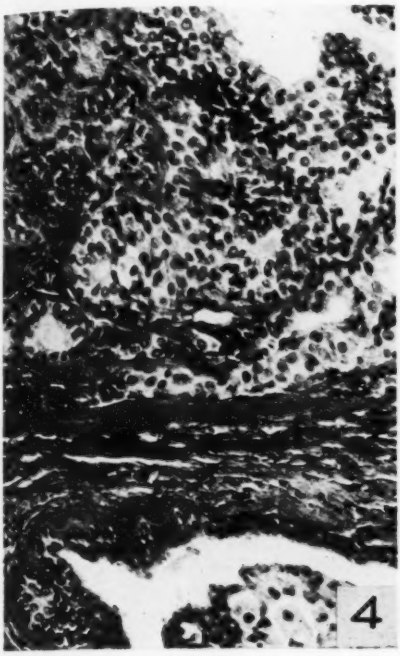
PLATE 71

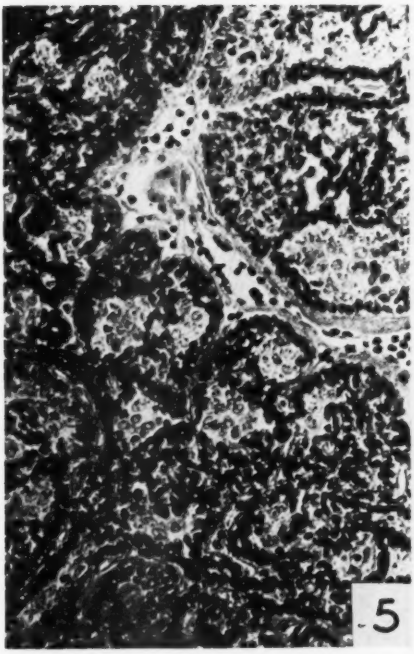
FIG. 4. Hydradenoma papilliferum. Clear reticulated cells resembling sebaceous cells are seen in the lower right-hand corner. Tumor had been present on the neck since childhood and measured 2 cm. in diameter. Phosphotungstic acid hematoxylin stain. × 265.

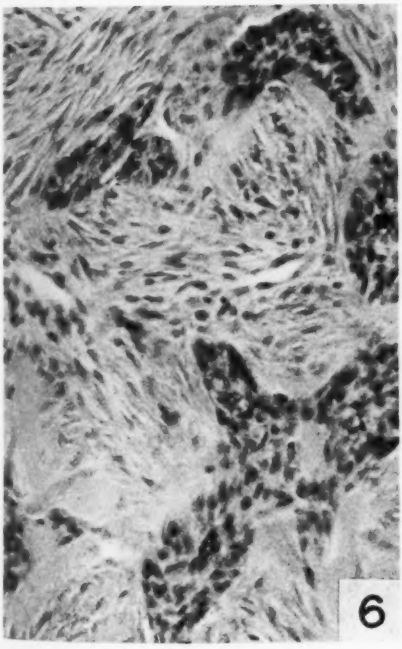
FIG. 5. Hydradenoma. There is an alveolar pattern. Pale cells are surrounded by darker smaller cells and there is an early hyaline deposit in the basement membrane. Phosphotungstic acid hematoxylin stain. × 265.

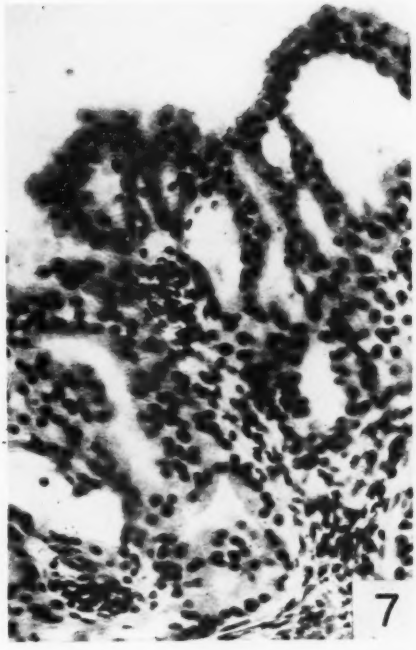
FIG. 6. Hydradenoid carcinoma. Hematoxylin and eosin stain. × 250.

FIG. 7. Hydradenoma papilliferum of apocrine gland. Hematoxylin and eosin stain. × 210.









Gates, Warren and Warvi Tumors of Sweat Glands

PLATE 72

FIG. 8. Hydradenoma papilliferum. The cavity of the lesion opens onto the surface at the upper right, and there is slight metaplasia of ducts and epithelium. Superficial type. Hematoxylin and eosin stain. × 165.

FIG. 9. Hydradenoma papilliferum. Intermediate type. Hematoxylin and eosin stain. × 165.

8

9

GYNANDROBLASTOMA OF THE OVARY*

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The term gynandroblastoma was first used by Robert Meyer [1] in 1930, in the discussion of a series of arrhenoblastomas reported by him, one of which had in part a histological similarity to granulosa cell tumor and was accompanied by uterine hypertrophy. He suggested that ovarian tumors may arise from indifferent elements which become morphologically and functionally hermaphroditic so that they may cause both hypertrophy of the uterus and masculinization.

Plate,[2] in 1938, collected 12 cases from the literature, which he believed could be placed in this category, and added one of his own. The tumor in his case had both granulosa cell and arrhenoblastoma elements, partly separated, but with visible transitions between them. He distinguished this tumor on histogenetic and morphological grounds from granulosa cell tumors and arrhenoblastomas.

No collected data concerning the biological effects of such tumors exist, but as certain clinical and pathological differences from the arrhenoblastomas might be expected to occur, we have reviewed the cases cited by Plate [2] together with other pertinent cases in an effort to determine whether or not such a distinction is supported by biological evidence, in connection with the additional case herein reported.

Although Plate's [2] reference is to Meyer's [1] case 6, it is his case 7 to which Meyer referred in his use of the term gynandroblastoma. Meyer stated, however, that his cases 6 and 7 are very similar and belong to the same group, with identical masculinizing features.

The following case was originally considered as an arrhenoblastoma, but the diagnosis was later changed to gynandroblastoma on the basis of both clinical and histological evidence.

REPORT OF CASE

The patient, a white woman, 24 years of age, came to the hospital seeking relief from lower abdominal pain and continuous vaginal bleeding of 10 days' duration. Menstruation began at 14 years and had always been regular, with 28-day intervals until the last 4 months before hospital admission, when she had flowed for 5 to 7 days about every 2 weeks. She was married at 18 years of age, with one pregnancy ending in abortion. She was divorced at 20 years and had remarried 5 months before hospital admission. Libido had never been strong. Physical examination revealed hirsutism with male voice and beard, acne vulgaris and hypertrophy of the

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clitoris, these changes having developed in the past 5 years. The breasts were slightly pendulous but not atrophic (Figs. 1 and 2). Her blood pressure was 118, systolic; 85, diastolic. A large pelvic tumor was palpable on the left side. A single 24-hour urine specimen collected before operation was tested for androgenic hormone by Dr. R. G. Gustavson, using the rat seminal vesicle method, with negative results. He also extracted approximately one-half of the tumor and tested the extract for androgenic effect, in the same way, with negative results.

At operation (by E. A. M.) the tumor was found to be associated with the left ovary. It was encapsulated but adherent to the posterior pelvic wall. Removal of the tumor together with the left adnexa was effected. The uterus was large and soft. The right ovary was small. Recovery was uneventful.

Following the operation vaginal bleeding ceased. Curettage was not performed. A normal menstrual period occurred 1 month after operation and menstruation has been normal since that time, for 3 years. The patient has been well except for one attack of pyelitis.

At the present time her voice is less hoarse than formerly but is still deep in pitch. The clitoris remains hypertrophied. Hair growth on the face and legs is less rapid and not so conspicuous. She has gained about 15 pounds and notes that her breasts are now less pendulous (Fig. 3).

Pathological Description

The tumor was spheroidal, 11 cm. in diameter, and weighed 349 gm. It was enclosed in a smooth fibrous capsule which was intact except for a roughened area 2 cm. in diameter where the tumor was adherent to the pelvic peritoneum.

The fallopian tube and ovary were attached to the tumor. The tubal attachment consisted of the mesosalpinx, while the ovary was incorporated in the capsule of the tumor, indicating that the tumor was situated in the mesovarium. The ovary was compressed into the form of a cap measuring 4.5 cm. in diameter, by 2 cm. in thickness at the center, tapering toward the edges, where the tunica albuginea became continuous with the capsule of the tumor.

Surfaces made by cutting through the ovary and tumor showed the ovarian cortex to be thin, grayish white, and solid except for several small cysts filled with clear fluid. Numerous cysts, ranging from less than 0.1 cm. to 0.4 cm. in diameter, and containing thick, turbid gray secretion, were present immediately beneath the capsule, at its junction with the tunica albuginea. These became less numerous and disappeared from the capsule entirely about 5 cm. beyond the junction ring. The substance of the tumor was solid, soft and moderately friable. It was coarsely mottled with pale yellow and white areas, and the central portion, comprising about one-third of the tumor, was dark purplish red as the result of hemorrhagic infiltration (Fig. 4).

Microscopical examination of paraffin sections of the ovary stained with hematoxylin and eosin disclosed numerous primordial follicles and a few developing follicles, but no corpora lutea. Corpora albicantia and

several small atretic follicular cysts were seen. The cortical stroma was scanty. The medulla was spread out, extending laterally to merge with the inner layer of fibrous tissue forming the capsule of the tumor. This layer was composed of loosely knit, thin collagenous fibers with interspersed fibrocytes. It carried numerous blood and lymphatic vessels and several nerve trunks.

Beginning within the medulla of the ovary and extending outward from the hilus along the inner layer of the capsule of the tumor there was a series of epithelium-lined tubules, corresponding to the cysts described grossly. They were of variable caliber and outline, some being distended with either granular or hyaline eosinophilic substance (Fig. 5). The epithelium was cuboidal in some and columnar in others. It was nonciliated but had a definite cuticular border. The cytoplasm was basophilic, with small vacuoles or with a single large vacuole located above the nucleus. The nuclei were large, oval and coarsely reticular. These tubules were located between the capsule and the substance of the tumor and did not extend into the deeper portion of the tumor.

The tumor was composed chiefly of more or less fusiform cells with large reticular nuclei containing much chromatin, and scanty basophilic cytoplasm, supported by a thin meshwork of fibrillary connective tissue, partially hyalinized in some areas, with many small blood vessels.

There was a distinct lobular arrangement throughout the entire tumor, the lobules being partly separated by thin fibrous septa. Viewed grossly or in low-power magnification the lobules were seen to differ in appearance, some being homogeneous and well circumscribed, while others were ragged in outline and uneven in density (Fig. 6). Under higher magnification the homogeneous lobules were found to consist of fusiform cells in poorly defined fascicular grouping with numerous zones in which the cells became polyhedral. The arrangement here resembled that of the relatively undifferentiated type of granulosa cell tumor (Fig. 7).

The other lobules were composed of similar cells but with distinctly different arrangement. In these, the cells formed tight whorls, solid cords with the cells curved across the long axis, or plicated tubules with incomplete lumina (Fig. 7). Transition zones between two types of lobules were quite frequent.

Groups of larger cells with abundant brownish red cytoplasm appeared in and about the second type of lobule. They resembled the interstitial cells of Leydig of the testis. In frozen sections stained with scharlach R they were found to contain lipoids in large quantity. Similar groups of lipoid-loaded cells were found in the connective tissue near the subcapsular epithelium-lined tubules (Fig. 5). In the homogeneous

lobules there were occasional individual cells containing lipoids, but they were smaller, with less cytoplasm, and the lipoid stained less intensely than in the interstitial cell groups. The necrotic portions of the tumor contained many small lipoid globules.

Sections stained by Masson's trichrome method and reticulum stains (Foot modification) did not serve to distinguish further cellular features.

Summary of Case

The clinical features of this case suggest a combination of the hormonal effects found in granulosa cell tumors and in arrhenoblastomas. It is to be noted that the patient continued to have recurrent uterine bleeding, without atrophy of the breasts and without loss of feminine body contour, during the time that hirsutism, voice changes and hypertrophy of the clitoris were developing. This is taken to indicate that both estrogenic and androgenic hormones were being elaborated by the tumor, with concurrent biological effects.

The histological structure of the tumor, with its distinctive lobular forms resembling granulosa cell tumor and arrhenoblastoma respectively, supports the biological evidence.

Bio-assay of the tumor substance and of the patient's urine failed to reveal the presence of androgenic hormone. However, since androgenic effects were well defined in the patient, it may be assumed that insufficient quantities of test material were supplied. The prompt re-establishment of normal menstrual function proves that the tumor was responsible for its disturbance. Hirsutism has diminished but has not disappeared. The voice remains masculine, and the hypertrophy of the clitoris persists.

The peripherally located tubules lined by columnar epithelium found in and near the hilus of the ovary are distinct from the rete ovarii. They are not characteristic of either granulosa cell tumors or arrhenoblastomas but have been noted before in arrhenoblastoma by Kanter and Klawans [3] together with embryonic rete, tissue resembling spermatic ducts, mesenchyme and cartilage.

The presence of interstitial (Leydig) cell groups also has been noted in arrhenoblastomas (Kanter and Klawans [3] and Novak [4]) although, according to Novak, their presence or absence does not always parallel that of virilism. These cells contain abundant lipoids and do not resemble degenerating cells undergoing fatty metamorphosis. It seems probable that they are concerned with elaboration or storage of the androgenic hormone. Stewart, Bell and Roehlke [5] have shown the relationship of interstitial cell tumors of the testicle to the development of secondary sexual characteristics of the male.

Review of the Literature

The original publications referred to by Plate [2] were reviewed. Additional cases, such as those reported by Bergstrand,[6] were also studied in order to determine if possible whether any constant clinical features were common to these cases, and whether special histological characteristics could be found. No attempt was made to include all the reported cases of granulosa cell tumor and of arrhenoblastoma.

In several of the cases clinical data were lacking, and in others histological description was incomplete. The available data are included in the following summary.

Meyer, R.,[1] Case 6

Age. 25 years.

Menstrual History. Menstruation regular, 3 days with pain. Thyroid operation at 25 years, followed by amenorrhea for 2 years. Hemorrhage of 8 days' duration recurred 1 month later, with rapid increase of size of abdomen.

Pregnancies. Not stated.

Masculinization. Marked increase in hair growth, male distribution, all over body. Beard grew fast. Voice rough and lower. Clitoris hypertrophied. Body slender and emaciated. Vagina narrow and firm.

Postoperative Condition. Decrease in hair growth. Menstruation returned after 4 weeks and remained regular. Voice more feminine. Libido returned to normal.

Ovarian Tumor. Right, kidney-shaped, smooth, adherent, weight 4,450 gm. In one small, firm part there was one large cyst and multiple small cysts. There were also a few solid accumulations, yellow or dark red. Slides showed loose fibrous areas with uncharacteristic strands and small cysts with low epithelium. In most places epithelial strands subsided into loose sarcoma-like proliferation. The epithelia were characterized by very irregular forms influenced by surroundings. Single cells, then many cells, became excavated, forming cysts. This peculiar cyst formation was considered important and partly due to softening within sarcoma-like cell proliferations. In another part, small and large cysts were embedded in a network of delicate moist connective tissue without solid cellular proliferation. There were many connections between cystic areas and solid areas containing cysts. Therefore, the question was raised whether the cysts arose within areas of solid proliferation or from strands of similar epithelium, or were they a peculiar part of the tumor with a different origin? The better preserved epithelial cells, especially the cylindrical, gave a mucin reaction. The solid epithelial strands contained small cavities and were, moreover, in connection with the spaces lined by mucinous epithelium. There was no transition from solid tumor into mucoid epithelial cysts and no evidence of transformation of areas with mucoid epithelium into solid strands. Meyer believed that originally two separate parts must have existed. The formation of mucous cysts could not be compared to pseudomucinous cystadenoma. Cell forms were different, papillae were lacking, mucus was not abundant.

Uterus and Adnexa. Uterus and left ovary, atrophic.

Meyer, R.,[1] Case 7

Age. 35 years.

Menstrual History. Began at 16 years. Regular for 6 years, then irregular. Four children. Menstruation ceased for 6 years after fourth childbirth. Irregular hemorrhage and almost continuous bleeding in past 9 months.

Masculinization. Voice low-pitched, hirsutism.

Postoperative Condition. Voice low, hirsutism gone, breasts normal, libido normal.

Ovarian Tumor. Right, size of fist, firm, partly hemorrhagic. Solid cell cords and large epithelial areas interspersed with larger vessels with much connective tissue. Resembled the granulosa cell type.

Uterus and Adnexa. Uterus removed with the tumor. Hypertrophy of corpus uteri. No histological examination.

Tietze,[7] Case 10

Age. 57 years.

Menstrual History. Amenorrhea from 40 to 50 years of age. Then menstruated regularly for 7 years. Last menstruation 4½ months before admission.

Pregnancies. Five, the last 25 years before.

Masculinization. None.

Ovarian Tumor. Left, cut surface showed central, firm, whitish tumor, hazel-nut sized. Fusiform and polyhedral cells in islands. Cell types were readily distinguishable, but there were transitions.

Uterus and Adnexa. Preoperative curettage showed cystic glandular hyperplasia of the endometrium. Total hysterectomy, uterus normal size, with high mucosa, hemorrhagic. Right ovary senile.

Tietze,[7] Case 11

Age. 76 years.

Menstrual History. Menses regular, menopause in 1904. Slight hemorrhages in 1924, subsiding after removal of polyps of the cervix. Slight hemorrhages in April, 1928, increasing after 2 months.

Pregnancies. Four.

Masculinization. Not described.

Postoperative Condition. Not described.

Ovarian Tumor. Left, size of hen's egg, solid. Right, firm tumor size of goose egg (fibroma). Left ovarian tumor made up of closely packed polyhedral cells and small groups of lighter cells between them.

Uterus and Adnexa. Size not stated. Myomatous nodules present. Endometrial polyps. Endometrium hyperplastic, with cysts.

Tietze,[7] Case 12

Age. 74 years.

Menstrual History. Menopause 24 years before. Periodic slight hemorrhages lasting 3 to 4 days at irregular intervals for about 6 months.

Pregnancies. 11 births, 2 abortions.

Masculinization. Not described.

Postoperative Condition. Not stated.

Ovarian Tumor. Left, size of walnut, soft, white, with two parts, one densely packed with sarcoma-like cells with little connective tissue, the other with many gland-like lumina in large or small groups. There were transitions from one part to the other and a few follicle-like structures were present.

Uterus and Adnexa. Uterus size of fist, two nodes resembling myomas, two endometrial polyps.

Amati,[8] Single Case

Age. 27 years.

Menstrual History. Amenorrhea complete for 5 years. Blood loss of the menstrual type then became re-established, becoming very abundant and accompanied by abdominal pain.

Pregnancies. None. Patient was virginal.

Masculinization. None.

Postoperative Condition. Dead.

Ovarian Tumor. Left, in part resembling testicular adenoma tubulare, in part lobular with islets and cysts resembling graafian follicles. Solid carcinoma with large cells and ovarian adenoma tubulare found united, for the first time, in this case. Not an ovotestis but a blastoma of germinal epithelium in a broad sense.

Uterus and Adnexa. Uterine mucosa presented characteristic pregravid modifications, with a wide decidual zone.

Schiller,[9] Case 3

Age. 22 years.

Menstrual History. Began at 15 years, regular. Then irregular for 3 years, sometimes missing for several months, very scanty. Last period 7 months before.

Pregnancies. None.

Masculinization. Marked hairiness of chin, chest, and about umbilicus. Breasts very small. Face had masculine appearance.

Postoperative Condition. Recovery. Ten years later, genitalia normal, regular menstruation of 4 days' duration.

Ovarian Tumor. Left, cystic, size of child's head. Tumor half cystic, half soft hemorrhagic tissue with small islands, trabeculae and follicular zones with central cavities.

Uterus and Adnexa. Uterus not described, right ovary normal.

Schiller,[9] Case 4

Age. 25 years.

Menstrual History. Regular until 2 years before. Irregular for 1 year. Amenorrhea for 1 year.

Pregnancies. Not stated.

Masculinization. Gain in weight (56 Kg.). Slight hypertrichosis, pubic hair slightly of male type.

Postoperative Condition. Recovery with loss of weight. Two months postoperatively, menstruation of 1 day's duration. Progynon given for 1 month, with menstruation for 4 days, followed by amenorrhea with increase in weight. Condition remained the same. No menstruation without medication.

Ovarian Tumor. Right, size of apple, yellow, firm, homogeneous. Partly composed of solid cells in hyaline connective tissue. Epithelial cells with round nuclei formed Call-Exner corpuscles similar to granulosa cell masses in other cases.

Uterus and Adnexa. Uterus not described. The left ovary contained a cyst the size of a goose egg, resembling the pseudomucinous variety. Cyst, only, was removed.

Schiller,[9] Case 11

Age. 37 years.

Menstrual History. Began at 14 years and became irregular after birth of second child 13 years ago. Menstruation became more and more rare. In past 2 years only two menstruations.

Pregnancies. Two.

Masculinization. Trace of brown mustache, almost male voice.

Postoperative Condition. Recovery, well after 9 years. Had uterine myoma.

Ovarian Tumor. Right, size of an apple. Ascites. Tumor was trabecular with oval cells with epithelioid nuclei. Transition between fibrous and cellular areas. Call-Exner arrangement of cells present. Similar to mature granulosa.

Uterus and Adnexa. Not described.

Eerland and Vos,[10] Case 2

Age. 35 years.
Menstrual History. Menopause 2 years before.
Pregnancies. Two children.
Masculinization. Virile body build, beard, male type of pubic hair, large clitoris.
Postoperative Condition. Menstruation set in 5 weeks after operation.
Ovarian Tumor. Right, size of child's head, believed to be arrhenoblastoma on grounds of clinical features, but resembling granulosa cell tumor histologically. Histological picture failed to reveal distinct tubular structures. Not entirely like other granulosa cell tumors with masculinization; in fact it was not to be distinguished from granulosa cell tumors without masculinizing features.
Uterus and Adnexa. Not described.

Eerland and Vos,[10] Case 5

Age. 40 years.
Menstrual History. Menopause for years.
Pregnancies. Yes, number not stated.
Masculinization. Beard.
Postoperative Condition. Soon after operation growth of hair on the face disappeared and menstruation set in.
Ovarian Tumor. Right, solid, size of child's head. Solid, trabecular and folliculoid parts. Granulosa cell tumor or andreioblastoma?
Uterus and Adnexa. Not described.

Eerland and Vos,[10] Case 13

Age. 45 years.
Menstrual History. Not stated.
Pregnancies. Not known.
Masculinization. Not described.
Postoperative Condition. Not described.
Ovarian Tumor. Left, only pieces examined. Solid tumor, both diffuse large cellular masses as in granulosa cell tumor and alveoli composed of larger light cells in epithelioid arrangement. Andreioblastoma(?). Malignant(?).

Frankl,[11] Single Case

Age. Young.
Menstrual History. Not stated.
Pregnancies. Not stated.
Masculinization. Markedly virilized.
Postoperative Condition. Not described.
Ovarian Tumor. Cystic, at first appeared to be a polycystic granulosa cell tumor. Only on examination of many areas was a small number of cords found comparable to those in arrhenoblastomas, the bulk consisting of granulosa cell tumor.
Uterus and Adnexa. Not described.

Bergstrand,[6] Case 1

Age. 22 years.
Menstrual History. Began at 13 years, regular until age 20, then ceased.
Pregnancies. None.
Masculinization. Hirsutism appeared at the time menses ceased.
Postoperative Condition. Not stated.
Ovarian Tumor. Two ovarian tumors shaped like ovaries, cystic. Made up of cells similar to granulosa cells in smaller or larger units with cysts. Some in the form of cell cords. Cystic units had definite follicular character, many converted

into corpora atretica. Ova were found in some cysts. No corpus luteum tissue was found, but in large cysts there were intensely yellow nodes in the walls resembling corpus luteum. The cells contained fat, not found in other cells.

Uterus and Adnexa. Not described.

Bergstrand,[6] Case 2 (Berner's)

Age. Not stated.

Menstrual History. Not stated.

Pregnancies. Not stated.

Masculinization. Hirsutism.

Postoperative Condition. Not stated.

Ovarian Tumor. Tubular structures interspersed with lipoid-containing cells, yellow color. Epithelial cells forming small cysts. Corpora atretica not seen.

Uterus and Adnexa. Not described.

Bergstrand,[6] Case 3 (Strassman's)

Age. Not stated.

Menstrual History. Not stated.

Pregnancies. Not stated

Masculinization. Hirsutism.

Postoperative Condition. Not stated.

Ovarian Tumor. Made up partly of tubules, partly of solid narrow cords of epithelial cells, and, between these, large lipoid-containing interstitial cells were present. The epithelial cells had undergone fatty metamorphosis to a certain degree and were not readily distinguishable from interstitial cells. There were many mitoses. Large hyaline areas like corpora atretica were found, but identity could not be proved.

Uterus and Adnexa. Not described.

Bergstrand,[6] Case 4

Age. 37 years.

Menstrual History. Menses ceased 2 years before hirsutism appeared.

Pregnancies. One child.

Masculinization. Hirsutism.

Ovarian Tumor. Right, size of hen's egg. Round, yellow focus, size of walnut, and several cysts filled with brownish red masses. Very complex microscopically. The walnut-sized focus was made up of mucus-producing cylindrical epithelium surrounded by cellular connective tissue, similar to normal uterine mucosa; gave the impression of malformation of Müller's duct. No smooth muscle was present. Elsewhere the tumor was quite different, with large accumulations of two types of cells, with cysts. One cell type was large, rich in cytoplasm with large, round nuclei. The other was a small dark cell poor in cytoplasm. The dark cells formed garlands, with necrosis and hyalin.

Uterus and Adnexa. Left ovary slightly enlarged, contained small cysts.

Bergstrand,[6] Case 5

Age. 17 years.

Menstrual History. Had never menstruated.

Masculinization. Hirsutism, voice change.

Postoperative Condition. Died 5 months after operation, with peritoneal metastases.

Ovarian Tumor. Right, size of child's head, soft, white. Left ovary similar but smaller. Bulk of tumor was made up of epithelium-like cells growing in diffuse masses separated by fibrous cords, with strand-like arrangement in some areas. Nuclei were vesicular, rich in chromatin with large nucleoli, relatively small amount

of cytoplasm. There were many mitoses. Cells of another form appeared lighter, with smaller nuclei. These were grouped about vessels, frequently showing fatty metamorphosis. The cytoplasm was variable. These cells resembled lymphocytes, but were not lymphocytes. Some cells formed garlands and tubules, and produced mucin. Similar conditions as in case 4, but not as clear-cut.

Uterus and Adnexa. Uterus not described. Left ovary not described further.

Bergstrand,[6] Case 6

Age. 22 years.

Menstrual History. Had never menstruated.

Masculinization. Hirsutism was present.

Postoperative Condition. Alive 9 years after operation. Hirsutism less, but had not entirely disappeared.

Ovarian Tumor. Right, mucinous cystadenoma size of man's head, lined by cylindrical mucoid epithelium. At one spot there was a dense accumulation of cells resembling lymphocytes and macrophages, very similar to case 5 (seminoma-like). Hyaline bodies similar to corpora atretica, stroma similar to that of ovary.

Felicissimo Paula Xavier and de Abreu Junqueira,[12] Single Case

Age. 34 years.

Menstrual History. Began at 14 years, more or less regular. Married for 15 years. Positive Wassermann test.

Pregnancies. Pain in abdomen with pregnancy, nausea of pregnancy. Tumor discovered at 5 months. Three children, four pregnancies; final pregnancy complicated by tumor.

Masculinization. Masculine habitus with male distribution of hair.

Postoperative Condition. Two months after removal of ovarian tumor stated that hair on face was growing rapidly and voice was worse. Was changed in appearance, with gross, acromegalic features, low harsh voice, beard, hypertrophy of larynx. Forearms hairy and rough. Acne pustules on face, back and chest, clitoris hypertrophied. Painful tumor in left iliac fossa. Fetus active. A verrucous nevus on anterior abdominal wall had become hypertrophied and hairy. Albuminuria and hypertension with edema. Premature rupture of membranes, fetal death, craniotomy. Fetus was female, masculinized, with hypospadiac clitoris. Maternal death.

Ovarian Tumor. Right, firm, solid, encapsulated, 9 by 5.5 by 4 cm. Some parts resembled adenoma tubulare, some with lumina, some solid cords. Cells in lymphatics of the pedicle. Corresponds to Meyer's arrhenoblastoma, group 2 (mixed type).

Uterus and Adnexa. Not described.

Plate,[2] Single Case

Age. 26 years.

Menstrual History. Began at 14 years, regular until 2 years and 9 months before, when periods of amenorrhea occurred lasting 4 to 5 months, ending in a hemorrhage longer and more severe than a normal menstrual period. Prior to admission there had been amenorrhea for 11 months. Married but never pregnant.

Masculinization. When the menstrual disturbances began, a growth of hair appeared upon the face, and the voice became deeper. Physical examination revealed that the mammae were well developed. Hair on abdomen was of masculine type. The voice was conspicuously deep. Clitoris and vagina were normal in size and consistence. The uterus was displaced to the right by a firm lump in the left half of the pelvis.

Postoperative Condition. Recovery. Menstruated normally 1 month after operation. The amount of hair on the face diminished but remained unchanged on the abdomen. The voice was deep.

Ovarian Tumor. Left, yellow on section. Cavity filled with a coagulated mass of clear yellow color. A structure the size of a cherry on one pole resembled a corpus luteum. Between the cavity and this structure were islets of intense yellow color. Microscopically, strands and islets resembling granulosa cells in folliculoid arrangement merged with tubules. Tubules were lined with low cylindrical epithelium. The cavity was lined with granulosa cells. The adenomatous portion corresponded with the patches of intense yellow color seen grossly.

Uterus and Adnexa. Curettage taken 7 days after operation showed practically normal endometrium.

If biological evidence of retained estrogenic activity plus masculinization is used as the criterion, not all of these cases fit into the category of gynandroblastoma. Histological evidence is not well enough defined to enable us to depend upon it for classification. Meyer's [1] cases 6 and 7 meet the requirement. The three cases of Tietze [7] all show evidence of estrogenic activity by the tumors, in spite of the fact that in case 10 there was amenorrhea for 10 years, but evidence of masculinization is not recorded. All three tumors contained heterogeneous cell types. Amati's [8] case also lacked signs of masculinization, although there was complete amenorrhea for 5 years, and the tumor in part resembled testicular adenoma tubulare. In all three of Schiller's [9] cases menstruation was normally established, then became irregular with final amenorrhea. Masculinization was not complete. All three tumors were cystic and more nearly resembled granulosa cell tumors than arrhenoblastomas.

In Eerland and Vos' [10] case 2 the patient was amenorrheic, showed masculinization and began to menstruate 5 weeks after operation. Here the case history is that of arrhenoblastoma, but the tumor was not to be distinguished histologically from granulosa cell tumor. In their case 5, the patient was amenorrheic, with a beard. Menstruation returned soon after operation and growth of hair on the face disappeared. The tumor was composite and if the biological evidence of amenorrhea is omitted it may be considered as a gynandroblastoma. Their case 13 lacks sufficient data for analysis.

Frankl's [11] case appears to belong in this category, although the menstrual history was not given.

Bergstrand's [6] cases, while not included by Plate,[2] seem to be pertinent to the problem. In all five there was hirsutism. In case 1 the menses ceased at the time hirsutism appeared. In cases 2 and 3 the menstrual history was not stated. In case 4 the menses ceased 2 years before hirsutism appeared. In cases 5 and 6 the patients had never menstruated. In case 1 there were bilateral cystic tumors with structures resembling corpus luteum and granulosa cells. In cases 2 and 3 the tumors were partly tubular with interspersed lipoid-containing

cells. These tumors answer the description of arrhenoblastomas. Case 4 was a complex tumor containing mucus-producing epithelium together with two other cell types, one of which was large and rich in cytoplasm with large round nuclei; the other was small, dark, poor in cytoplasm and formed garlands. In case 5 tumors were bilateral, larger on the right, and in part the structure suggested seminoma. These cases are suggestive of dysgerminoma, but with masculinizing effect due to an unidentified androgenic component. Case 6 is a cystic tumor with characteristics of pseudomucinous cystadenoma but with accumulations of cells of lymphocytic and macrophage type, similar to those in case 5.

Plate's [2] case is significant clinically and presents a complex histological structure consistent with both granulosa cell tumor and arrhenoblastoma. Through the courtesy of Dr. Walter Schiller, Cook County Hospital, Chicago, we have had an opportunity to study sections of this tumor. Interstitial cells in small groups were present but were not numerous. Lipoid storage was not prominent in any of the cellular elements. Mucus-secreting epithelium was not found in the sections available.

Schiller [13] accepted only three cases in Plate's [2] series as gynandroblastomas. These were Plate's, Frankl's, and Schiller's case 4. Schiller [14] has published a detailed description of his case, interpreting it as a gynandroblastoma. In addition to these three and the present case, Schiller cited the unpublished case of Christopoulos for inclusion in this group.

The case of Felicissimo Paula Xavier and de Abreu Junqueira,[12] while classified as arrhenoblastoma, is included because it illustrates androgenic effects in pregnancy not previously demonstrated in women but paralleling those produced experimentally in animals (Greene, Burrill and Ivy [15]). Developing during the course of pregnancy, the tumor was removed at 5 months but recurred within 2 months and resulted in masculinization of the mother and of the female fetus, which was delivered instrumentally near term.

Comment

Ovarian tumors exist in which there is alteration of the secondary sexual characters of the bearer in the male direction, presumably as a result of the androgenic hormone liberated by the tumor; but at the same time there is a continuation of cyclic menstrual bleeding, with indications of hyperestrinism. Such cases differ from granulosa cell tumors both biologically and histologically. Robert Meyer [1] first applied the term gynandroblastoma to them. There is no constant cell

pattern in these cases, and they appear to represent combinations of granulosa cell tumors and arrhenoblastomas. The presence of tubular structures lined by cylindrical, mucus-secreting epithelium has been noted in these, as well as in arrhenoblastomas and in the seminoma-like tumors of Bergstrand.[6] Interstitial cells carrying lipoids, resembling the testicular Leydig cells, are common to both gynandroblastomas and arrhenoblastomas. There is presumptive evidence that these cells are the source of the androgenic hormone.

The question of antagonism between androgenic and estrogenic hormones in gynandroblastomas is complex. Androgenic hormones are capable of inhibiting menstruation in the normal woman, theoretically by inhibiting the gonadotrophic factor of the hypophysis, thereby preventing ovarian formation of estrin. This does not apply in case of the tumor, necessarily, as the tumor cells may be able to produce estrin independently of hypophyseal factors. Therefore, hyperestrinism and virilism may co-exist in the same person. It is possible also that hormones produced by tumors may differ from those originating normally in the gonads after puberty, both chemically and in their physiological effects. Frankl [11] mentioned Halban's theory that persons who become masculinized possess a latent intersexuality necessary to respond to the presence of androgenic hormone. Clinical experience with therapeutically administered androgenic hormones, as reported by Geist, Salmon, Gaines and Walter,[16] and by Greenhill and Freed,[17] does not prove the theory of a restricted latent intersexuality, but indicates that latent intersexuality, in the sense of possession of receptors for the androgenic hormones, if not universal must be very common. From the work of Geist and co-authors it appears that doses of less than 200 mg. of testosterone propionate do not suppress menstruation or cause any demonstrable changes in endometrium or vaginal smears, while larger doses (more than 500 mg. per month) produce some or all of the following effects: temporary amenorrhea, senile vaginitis, hoarseness, hirsuties, acne and enlargement of the clitoris.

Bergstrand [6] rejected all earlier theories, ascribing hirsutism to the internal secretion of tumors arising in an hypothetical testicular component of the embryonic ovary. He found no indication from his studies whether the hormone is produced by the granulosa or the lutein cells of the tumors, but subscribed to the theory of Steinach and Kun that the hormone comes from the lutein cells. At least two and possibly three of his cases are of great interest in that combinations of androgenic components with dysgerminoma are suggested by the descriptions. Sailer [18] has described granulosa cell nests in ovarian dysgerminoma. Ewing [19] has presented evidence that embryonal carcinoma of

the testicle is of teratomatous origin and L'Esperance [20] has shown the analogy between this and embryonal carcinoma of the ovary. The fact that testicular tumors of this type produce gonadotrophic hormone was first observed by Zondek [21] and has since been extensively studied by Ferguson [22] and further amplified by Twombly, Temple and Dean,[23] who found little correlation between the amount of gonadotrophic hormone in the urine and the histological type of the tumor. It may be considered, however, a strong indication of the teratomatous nature of such tumors.

The opinion of Krock and Wolferman [24] that arrhenoblastomas do not constitute a pathological entity but represent teratomas containing virilizing elements is borne out equally well in gynandroblastomas, in which histological structure is also variable.

Conclusion

The term gynandroblastoma may be usefully applied to describe a clinical-pathological syndrome, but there is no constant accompanying histological pattern. The ovarian tumor concerned has epithelium-lined tubules and interstitial cell groups in common with arrhenoblastoma. The impression is gained that combinations of granulosa cell tumor with arrhenoblastoma do occur but that one element or the other usually predominates to the extent that the double biological effect is lacking. It is suggested also that the gynandroblastomas are teratomatous.

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[*Illustrations follow*]

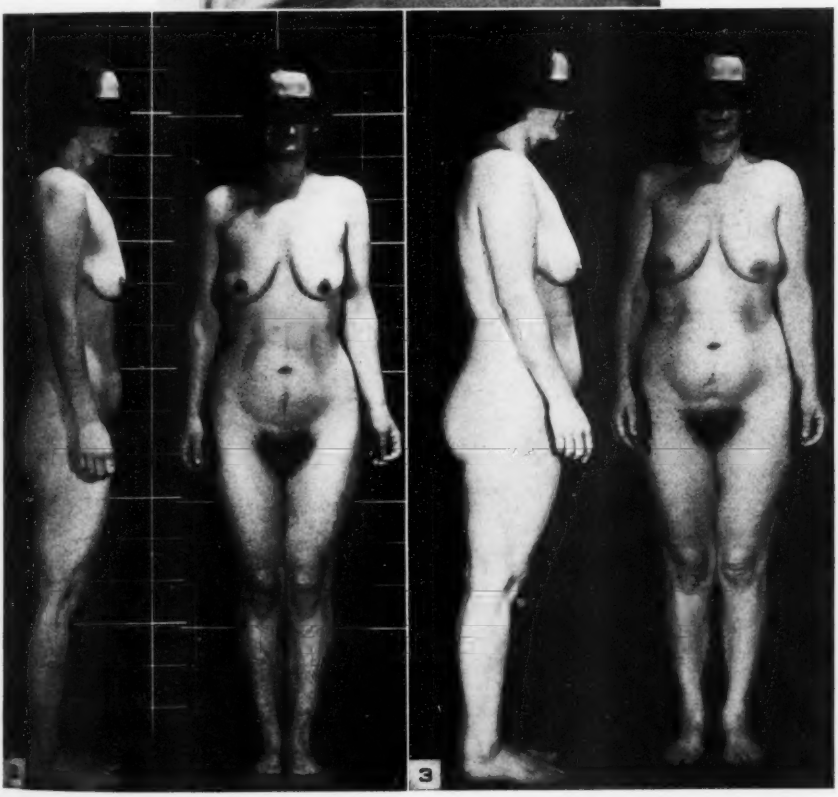
DESCRIPTION OF PLATES

PLATE 73

FIG. 1. Growth of beard and mustache 3 days after shaving.

FIG. 2. Physical appearance of the patient before operation, with hirsutism, acne vulgaris, a large larynx and pendulous breasts. The patient had shaved shortly before these pictures were taken.

FIG. 3. Gain in weight and reduction in hirsutism 6 months after operation.

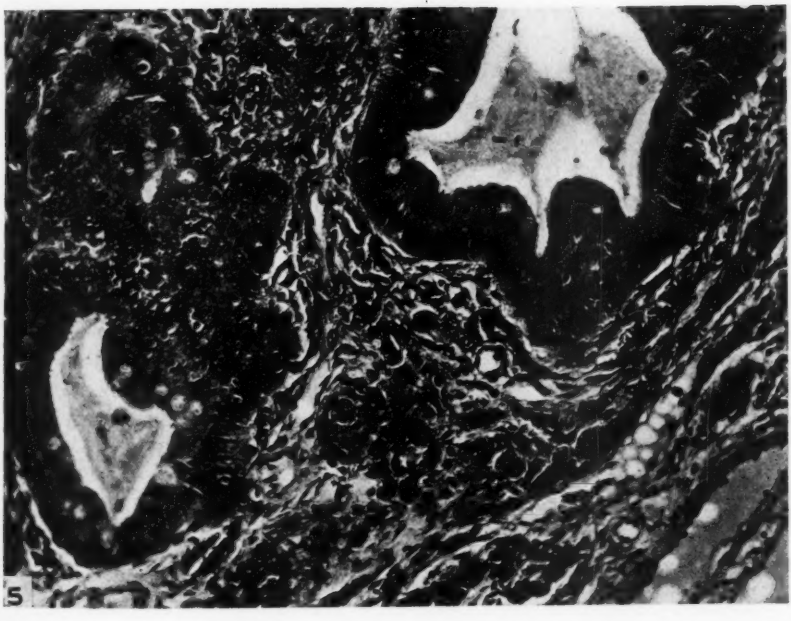


Mechler and Black Gynandroblastoma of the Ovary

PLATE 74

FIG. 4. The cut surface of the tumor and ovary.

FIG. 5. Epithelium-lined tubules and interstitial cell groups in the tumor. × 150.

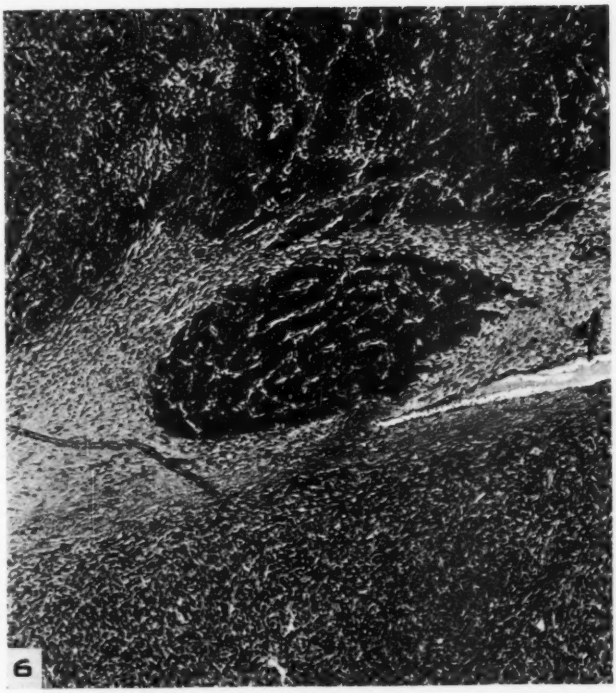


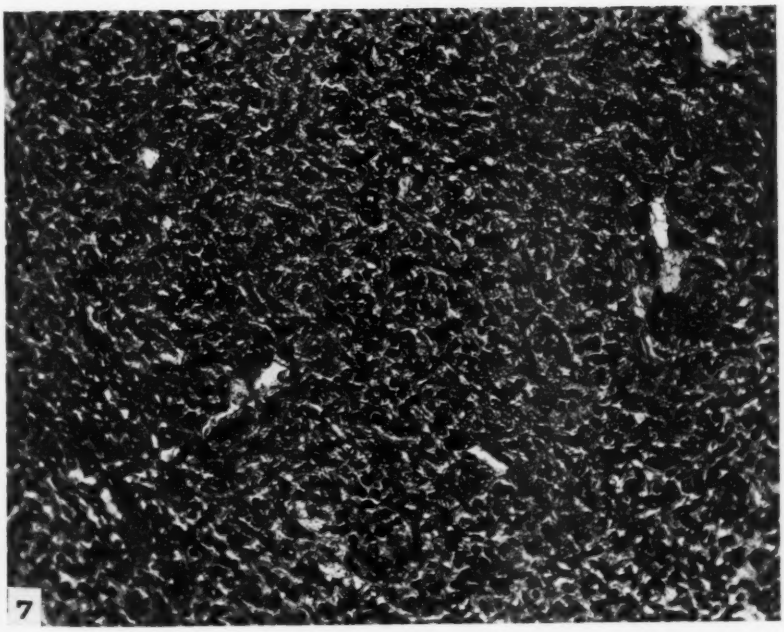
Mechler and Black Gynandroblastoma of the Ovary

PLATE 75

FIG. 6. Lobular forms with granulosa cell pattern at the bottom of the field and solid cords and whorls at the top. There is a central island of imperfect plicated tubules. × 75.

FIG. 7. A lobule of the tumor of granulosa cell type. × 150.





Mechler and Black Gynandroblastoma of the Ovary

STUDY OF SENSORY GANGLIA IN MACACA MULATTA AFTER GASTROINTESTINAL ADMINISTRATION OF POLIOMYELITIS VIRUS *

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In 1910, Leiner and von Wiesner [1] reported success in infecting the rhesus monkey with the virus of anterior poliomyelitis when it was administered by feeding. Since that time other attempts of a similar nature have been made with largely negative or equivocal results.[2-10] The virus has been fed, and given by stomach tube and by rectal tube, often with the introduction of accessory factors designed to improve the chances for infection; but experimental anterior poliomyelitis with paralysis and typical changes in the spinal cord has rarely resulted. The virus has, on occasion, been recovered from the feces of monkeys during a period when it was being fed intensively.[8, 9] In spite of this fact it is not clear from the literature whether in the rhesus monkey the barrier against infection via the gastrointestinal tract lies in the lumen of the tract or in its mucosa and wall. However, if the virus can survive at all in the lumen, it is conceivable that some agent or agents exist which might carry it across the mucosa and into contact with the nervous system.

In a previous report [11] the occurrence of certain lesions of the peripheral nervous system in experimental poliomyelitis is described. These lesions were present in the sensory ganglia of monkeys following intraperitoneal inoculation of human stool. No accompanying changes were observed in the central nervous system. When, therefore, experiments were planned to attempt to break the intestinal barrier against poliomyelitis virus, it was borne in mind that the end-point of the experiment might not be clinical paralysis with destruction of the anterior horn cell, but rather subclinical disease with some evidence of involvement in sensory ganglia.

GENERAL TECHNIC

Macaca mulatta were used; in the test group, animals weighing between 2200 and 2800 gm. were selected. No selection was practiced regarding sex. The period between the final administration of virus and sacrifice of the animals varied and is explained under each experiment. All sacrificed animals, both test and control, were killed by intracardiac injection of air and were autopsied immediately.

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In examining the central nervous system at least one block of tissue was taken from the sacral, one from the lumbar, three from the dorsal and one from the cervical region of the spinal cord. Three blocks were taken from the medulla oblongata, one from the mesencephalon, and three from the diencephalon. The paravertebral sympathetic chain from the stellate ganglion to the brim of the pelvis was taken from each side. Blocks of tissue were taken from each major division of the cerebral cortex and from the cerebellum.* Following the description of Howell and Straus [12] of the intervertebral ganglia, an attempt was made to recover seven pairs of cervical, twelve pairs of thoracic, seven pairs of lumbar, three pairs of sacral, but only three pairs of caudal ganglia; search for the last caudal pair was omitted. The ganglia, regarding segment and side, were identified throughout the subsequent procedures. Two vagal and two gasserian ganglia and both olfactory bulbs were recovered but not identified as to side.

All tissues were fixed immediately in 70 per cent ethyl alcohol, blocked in paraffin, cut at 10 μ, and stained with thionin. Obviously, the examination of the central nervous system was on a basis of sampling, but the peripheral ganglia and olfactory bulbs were cut serially and thoroughly scrutinized. Since the smallest lesions found extended through only three to five paraffin sections, an attempt was made never to lose more than two or three consecutive sections from any ribbon, but this aim could not always be achieved. The actual number of sections of spinal ganglia obtained from each animal is given in Table I. The examination of both test animals and controls was equally extensive and the observations are therefore believed to be comparable. In the actual microscopic study every second section was inspected and if suggestive changes were seen, adjacent sections were also examined (Figs. 1 to 16).

The Lesions

In severe experimental poliomyelitis in monkeys, lesions of the spinal ganglia are prominent and easily identified. Flexner and Lewis [4] described the main attributes, but they dealt principally with ganglia in which widespread destruction of nerve cells with marked inflammatory reaction was present. Early in the current investigations it became apparent that no such striking tissue alterations could be found. Inflammatory foci were rare and of minute proportions, usually involving, at the most, one or two neurons in an entire ganglionic mass and only

* Although changes were noted in the sympathetic ganglia, a description of these changes or of the tissues taken from the cerebral cortex where lesions were not observed is not given, since the examination could not be made in sufficient detail to warrant any conclusions being drawn.

occasionally as many as four or five neurons. Perivascular reactions were for the most part lacking and the interstitial spread of inflammatory cells was usually confined to the immediate vicinity of the nerve cell. Since cytologic alterations in neurons were not thought to be safe guides, it was often difficult to be certain that in a focal lesion a neuron had actually been destroyed. The inflammatory or non-nervous cells in a reaction were largely lymphocytic types, occasional polymorphonuclear cells were seen, and some cells resembling plasma cells were prominent, especially in the vagal ganglia. Sometimes, too, cells that might have been swollen pleomorphic forms of capsular cells seemed to dominate the picture. It is not intended to define here the exact identity of these cells, only to indicate that most of them were of mononuclear type.

If it is assumed that when the virus of poliomyelitis attacks the nervous system it acts primarily by destroying or altering neurons, then the smallest unit of pathologic change must be that accompanying the involvement of a single neuron. On this basis, and since no specific diagnostic sign is available, it was decided that in counting lesions, any cellular focus localized about a disintegrated or partially disintegrated nerve cell, or the site where a nerve cell might reasonably have been, must be considered as a lesion. This criterion has been held in examining all animals, both those exposed to the virus and those in which no known exposure had occurred. In Tables I to III no attempt is made to gauge the severity of lesions; only their presence or absence is indicated.

Experimental Procedure

Demme,[7] in some of his experiments, had used saponin to prepare the gastrointestinal tract for the virus. In a previous study [13] I have shown that Duponol,* a wetting agent, could be used in the presence of poliomyelitis virus to prepare stool specimens for intraperitoneal inoculation. It was hypothesized that because of its wetting properties such an agent might bring virus suspensions into more intimate contact with the intestinal mucosa and so facilitate the passage of the virus. If any of the lesions found during the first three experiments were due to the virus of poliomyelitis, there was little evidence that Duponol had altered the mechanism of infection.

First Experiment

A fresh passage of the Knox strain of poliomyelitis virus recovered from human feces [14] was made intracranially into an anesthetized monkey. This monkey was sacrificed as soon as severe paralysis appeared; the spinal cord and brain stem were

* Duponol W. A. (flakes), a sodium lauryl sulfate, manufactured by E. I. DuPont de Nemours & Co., Inc., Wilmington, Del.

TABLE I

*Lesions in the Peripheral Nervous System of Rhesus Monkeys after Gastric or Rectal Administration of Poliomyelitis Virus**

	Monkey no.	Inoculation	No. of spinal ganglia		No. of spinal ganglion sections seen	X nerve ganglia		V nerve ganglia		Olfactory bulbs		Clinical picture†
			Examined	With lesions		1	2	1	2	1	2	
First experiment: Knox strain, by stomach tube	245M	5% virus, 0.6% Duponol; 3 feedings, 25 ml.; regurgitated once	64	60		−	−	+		+	−	Poliomyelitis; killed 11th day
	235M	5% virus, 0.6% Duponol; 3 feedings, 25 ml.; vomited once	58	11	4,034	−	−	+	−	−	−	Fever(?); killed 13th day
	230M	5% virus; 3 feedings, 25 ml.	64	8	4,184	−	−			−	−	Uneventful; killed 20th day
Second experiment: Rockefeller M.V. strain, by rectal tube	248M	2% virus, 0.5% Duponol; 3 enemas, 115 ml.	63	1	3,697	−	−	−	−	−	−	Uneventful; killed 19th day
	250F	2% virus, 0.5% Duponol; 3 enemas, 110 ml.	64	8	2,308	+	−	−	−	−	−	Fever(?); killed 16th day
	174M	2% virus; 3 enemas, 100 ml.	64	16	3,481	+	−	+	−	−	−	Fever, diarrhea, tuberculosis; killed 19th day
Third experiment: Rockefeller M.V. strain, by rectal tube	285M	5%virus, 0.5 % Duponol; 3 enemas, 150 ml.	64	8	4,996	−	−	−	−	−	−	Uneventful; killed 12th day
	277M	5% virus; 3 enemas, 150 ml.	64	7	5,067	+	−	+	−	−	−	Uneventful; killed 12th day
Fourth experiment: Rockefeller M.V. strain, by rectal tube	322M	6% virus; 1 enema, 45 ml.; 1.5 mg. histamine, intravenously	64	13	6,798	+	−	−	−	−	−	Uneventful; killed 17th day
	330M	6% virus; 2 enemas, 90 ml.; 1.5 mg. histamine, intravenously; 2.0 mg. histamine, intravenously	64	18	7,528	+	+	+	−	−	−	Uneventful; killed 21st day
	328F	6% virus; 2 enemas, 90 ml.	64	9	7,013	+	−	+	+	−	−	Uneventful; killed 21st day

Fourth Rockefeller strain	328F	6% virus; 2 enemas, 90 ml.	64	9	7,013	+	−	+	+	−	−	Uneventful; killed 21st day
Rockefeller M.V. strain, by stomach tube	323M	20% virus; 1 feeding, 15 ml.; 2.0 mg. histamine, intravenously	63	7	6,700	−	−	−	−	−	−	Uneventful; killed 16th day
	326M	20% virus; 2 feedings, 30 ml.; 1.5 mg. histamine, intravenously; 2.0 mg. histamine, intravenously	64	9	5,225	−	−	+	+	−	−	Uneventful; killed 21st day
	325F	20% virus; 2 feedings, 30 ml.	64	3	6,104	+	+	−	−	−	−	Questionable; killed 22nd day
Control animals: Monkeys having no inoculation, sacrificed or dying of conditions other than poliomyelitis	292	None	64	−	3,752	−	−	−	−	−	−	Died; enteritis, *B. dysenteriae*
	293	None	57	1	4,205	+	−	−	−	−	−	Died; pneumonia
	331	None	63	−	4,596	−	−	−	−			Sacrificed; tuberculosis, *B. dysenteriae*
	391	None	64	2	7,968	+	−	−	−	−	−	Sacrificed; emaciated
	392	None	64	4	6,885	−	−	+	+	−	−	Sacrificed; tuberculosis
	394	None	64	2	9,015	−	−	−	−	−	−	Sacrificed; ill, emaciated
	395	None	64	−	8,237	−	−	−	−			Died; cause undetermined
	396	None	61	−	7,000	−	−	−	−	−	−	Sacrificed; ill

* The central nervous tissues and olfactory bulbs of all, excepting monkey 245, failed to show changes and hence are not listed in the tables.

† All times are figured from the date of first inoculation.

+ = Any lesion of whatever severity.

− = Structure was examined and no lesion seen.

A blank space indicates that the structure was not examined.

ground with sterile alundum and taken up in sterile distilled water to make a 5 per cent virus-cord suspension. The suspension was divided into three equal portions. To two of them Duponol was added in 0.6 per cent concentration. All three portions were stored at 4° to 8° C. when not in use.

Three monkeys were chosen and the suspensions were introduced by gastric tube on 3 successive days beginning on September 10, 1941, each animal receiving a total of 25 ml. Monkeys 245 and 235 were given Duponol-treated suspension; monkey 230, nontreated suspension.

On the first administration, monkey 245 regurgitated part of the feeding and in 7 days showed typical clinical signs of poliomyelitis with fever and paralysis. The classical lesions of experimental poliomyelitis were found in its spinal cord, brain stem, sixty of the spinal ganglia, one gasserian ganglion, and one olfactory bulb. Because of olfactory bulb involvement it must be assumed that the portal of entry was by way of the olfactory mucosa. This animal therefore is excluded from the percentage derivatives for sensory ganglia found in Table III.

Monkey 235 had a slight increase in temperature on the eighth day but showed no other signs of disease. Lesions were found in eleven spinal ganglia and in one fifth nerve ganglion.

Monkey 230 had an uneventful clinical course; eight spinal ganglia showed lesions.

Second Experiment

A month later, in October, 1941, a 2 per cent suspension in physiologic saline solution of a freshly passed virus of Rockefeller M. V. strain was divided as before into three parts. One part was left untreated and to the others two parts Duponol was added to make a 0.5 per cent concentration. Three monkeys were chosen and this time the virus suspensions were administered by a rubber tube, 6 to 8 inches of which was passed into the rectum. (See Tables I and II.)

Monkey 250 received on 3 successive days rectal inoculations totaling 110 ml. of Duponol-treated suspension. It showed questionable fever on the fifth and sixth days but no other clinical signs. Eight spinal and one vagal ganglia were involved.

Monkey 248 also received on 3 successive days inoculations totaling 115 ml. of Duponol-treated suspension and had an uneventful clinical course. A single minimal lesion was found in one spinal ganglion.

Monkey 174 was given on 3 successive days inoculations totaling about 100 ml. of untreated virus suspension. It had marked fever with some diarrhea on the 13th and 14th days and subnormal temperature on the 16th day. At autopsy mild tuberculosis was found. Sixteen spinal ganglia, one vagal ganglion, and one gasserian ganglion showed focal lesions.

Third Experiment

In December, 1941, after a number of control animals had been examined and it was apparent that some difference existed between them and the test animals, a third experiment was set up. The M. V. strain was freshly passed and the infected cord ground as before. The suspension this time was made in sterile distilled water to a 5 per cent concentration and divided into two portions. To one, Duponol up to 0.5 per cent was added; the other was untreated. Two monkeys were chosen and each received a rectal inoculation on 3 successive days. The total was 150 ml. per animal.

Monkey 285 was given the Duponol-treated suspension; it had an uneventful clinical course and eventually showed lesions in eight spinal ganglia.

Monkey 277 received untreated virus suspension. It showed no clinical signs of poliomyelitis and had involvement of one vagal and one gasserian ganglion, in addition to lesions in seven spinal ganglia.

Distribution by Segment and Side of Lesions in the Intervertebral Ganglia

	Monkey no.		Cervical							Dorsal												Lumbar							Sacral			Caudal			
			2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	1	2	3	1	2	3	4
Stomach tube	235	L		−	−	−	+	−	−	−	+	−	−	−	−	−	+	−	−	−	−	−	−	−	+	−	+	−	+	+	−	−			
		R		−	+	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−			
	230	L	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	+	−	−	−	−	+	+	−	−	
		R	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	+				
	323	L	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	+	−	−	+	+	−	+	−	−	−	−	−	−	
		R	−	−	−		−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	326	L	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	+	−	+	+	+	−	−	−	−	−	
		R	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−				
	325	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
Enema	248	L	−	−	−	−	−	−	−	−	−	−	−		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	1
		R	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				1
	250	L	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−				
	174	L	−	−	−	−	−	+	+	+	−	−	+	+	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	+	−	−	−	
		R	−	−	−	−	+	+	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	+	−	+	−	+	−	−	−				
	285	L	−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	
		R	−	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−				
	277	L	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−				
	322	L	−	+	−	−	−	+	+	+	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	
		R	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−				
	330	L	+	−	+	−	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	+	−	−	−	+	+	+	−	−	−	−	−	−	
		R	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−				
	328	L	−	−	−	−	+	−	−	+	−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	+	
		R	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−				
Controls	292	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	331	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	293	L		−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
		R		−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	392	L	−	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−				
	394	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	391	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	395	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
		R	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				
	396	L	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−		
		R	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−				

+ = Any lesion of whatever severity. − = Structure was examined and no lesion seen. A blank space indicates that the structure was not examined.

The frequency and distribution of lesions as given in the tables and the quality of the lesions as illustrated give some idea of the problem as it existed after the third experiment. In the tissue examinations the animals had not been treated as unknowns; that is, the examiner was aware which were test and which control animals. As a check, therefore, the sections from five test animals were selected by an assistant. These were re-examined as unknowns and with the exception of a single instance, the lesions were reidentified accurately.

Since it was conceived that the changes in the intestinal tract induced [15] by histamine shock might alter its barrier against the virus, a final experiment was planned in May, 1942, to test this idea, and to check previous experiments.

Fourth Experiment

Along with the examination of more control animals, Rockefeller M.V. strain was freshly passed as before, this time in two animals. After quadriplegia occurred they were sacrificed, histologic examinations were made for characteristic cord changes, and the cords and brain stems ground and suspended in sterile distilled water. The initial strength of this suspension was 20 per cent. It was divided in two parts. One part contained enough for five doses of 15 ml. The other part was diluted with sterile distilled water to make a 6 per cent suspension. The volume was sufficient for five doses of 45 ml. each.

Three monkeys were selected for gastric inoculation, three for rectal inoculation. It was known that the action of histamine might induce vomiting and defecation. The procedure of inoculation had therefore to be accommodated to these facts. In gastric inoculation food was withheld for 18 to 24 hours before intubation. After the introduction of the virus, the animals were hosed with tepid water and isolated. Three hours later histamine dihydrochloride was given intravenously and the monkey quickly placed in a separate cage until the reaction had ceased. It was then hosed thoroughly again and returned to its quarters. The cage where the reaction occurred was well cleaned. With this method, although retching occurred, no monkey vomited more than a small quantity of mucus.

The rectal inoculations were conducted similarly, although the interval between intubation and the exhibition of histamine was reduced to one-half hour. The interval was based on an estimate of the time required for spreading the inoculum over the lower bowel.

The histamine used was a commercial preparation of a 1:1000 solution of histamine dihydrochloride. In none of the animals inoculated was a severe reaction induced.

Monkey 322 was given one enema, 45 ml. of virus suspension, and one injection of histamine. The clinical course was uneventful and lesions were found in thirteen spinal ganglia and one vagal ganglion.

Monkey 330 was given two virus enemas, a total of 90 ml., and two injections of histamine. There were no clinical signs. Eighteen spinal ganglia, both vagal ganglia, and one gasserian ganglion showed lesions.

Monkey 328 was given two virus enemas, a total of 90 ml., but no histamine. There were no clinical signs. Nine spinal ganglia, one vagal ganglion, and both gasserian ganglia showed some involvement.

Monkey 323 was given one stomach feeding of 15 ml. of virus suspension, and one injection of histamine. No clinical signs were observed. Seven spinal ganglia showed lesions.

Monkey 326 was given two stomach feedings totaling 30 ml. of virus and two histamine injections. The clinical course was uneventful. Nine spinal and both gasserian ganglia proved to be involved.

Monkey 325 was given two stomach feedings of virus, a total of 30 ml., but no histamine. Questionable fever occurred. Examination of the nervous system showed three spinal and both vagal ganglia to be involved.

Lesions of the spinal ganglia were more frequent in animals receiving histamine; those given two inoculations, both of virus and histamine, had more lesions than those receiving one. The difference, however, is not so clear when one compares vagal or gasserian ganglia. These data do not seem sufficient to allow any conclusions regarding the activity of histamine in breaking the barrier against virus.

Controls

Since apparently healthy monkeys were at a premium, sick animals were chosen. Most of them were killed in the usual manner when it became evident that they were seriously ill. A few died and were autopsied up to within 6 hours after death. Animals that were thought to have been dead for a longer period were discarded. Signs of disease, though not necessarily the cause of death, were recorded. It was believed, moreover, that this control group represented the commoner disease pictures found in laboratory colonies of rhesus monkeys, and that nonspecific lesions of the nervous system would be more evident than in healthier animals.

In many of the animals no lesions could be found and in the others they were sparse, a total of thirteen ganglia in eight animals showing involvement.

Tables I and II give the number and distribution of the focal lesions. Table II contrasts the difference in the distribution of lesions in animals receiving stomach feedings and those given the virus by rectum. It demonstrates, too, that the differences are in the number of ganglia involved, but not in the distribution of the involvement.

Table III summarizes numerically Tables I and II and gives the percentage of involvement of sensory ganglia. The brain stem and olfactory bulbs are omitted since no lesions were observed in these regions.

TABLE III

Summary of Findings in Sensory Ganglia

Type of inoculation	Spinal ganglia		X nerve ganglia		V nerve ganglia		Percentage of ganglia with lesions		
	No. examined	No. with lesions	No. examined	No. with lesions	No. examined	No. with lesions	Spinal	X nerve	V nerve
Stomach tube	313	38	10	2	8	3	12	20	37
Enema	511	80	16	7	16	5	16	44	31
Control	501	9	16	2	16	2	2	12	12

DISCUSSION

The lesions described are for the most part very minute and by any criteria known to me are nonspecific. The significance of the observations therefore rests entirely upon the thoroughness of examination and the accuracy of identification of the lesions in test animals and controls.

Since no series of animals inoculated with sterile monkey cord was examined, the possibility that pathologic change in sensory ganglia might be produced by such inoculations cannot be excluded. That possibility seemed so remote, however, that it was thought inadvisable to expend animals for the purpose of determining it.

If it be allowed that most of the nerve cell destruction observed in the test animals was produced by poliomyelitis virus, then several features brought out in the tables are of interest. Firstly, *Macaca mulatta* actually may be infected via the gastrointestinal route. In future one may be better able to examine the natural limitations imposed on the infectious agent by this portal, or, in other words, to inquire more exactly what and where is the barrier.

Secondly, the increased frequency of lesions of the spinal ganglia in the lower cervical, lumbar and sacral segments as compared with the upper cervical, dorsal and caudal segments is striking, especially since the segments most often involved correspond quite closely to the portions of the spinal cord functioning for the extremities. One is tempted to read into this situation some peculiar "hook-up" of the sensory system with the intestinal tract, until it is recalled that the lower cervical and lumbosacral ganglia are the largest in the intervertebral series and may therefore contain more nerve cells. In the face of this, any basic distributing system could make more contacts in these ganglia and hence give greater chance for involvement. Both of these ideas rest on the assumption that the virus travels from the gut to the ganglia centripetally in nerve processes. Actually, at this time no explanation is offered of the mechanism accounting for the occurrence or distribution of lesions in either spinal or cranial nerve ganglia. However, I am familiar with some of the work [16] that describes the presence of unmyelinated fibers of the autonomic nervous system in the mucosa and submucosa of the bowel, and of unmyelinated nerve fibers, possibly sensory, ending in the epithelium itself.

Thirdly, when virus suspensions are put into the stomach of an animal, one might reasonably expect that if the agent survived it would eventually reach the rectum, having traversed the intervening tract. On the contrary, one would not expect virus put into the large bowel to reach the stomach or even most of the small intestine. Likewise, if in traversing the intestinal tract the virus particles were changed either as to quantity or infectivity, then one might anticipate slighter involvement from its inoculation into the stomach than into the colon. On examination of the tables of distribution for spinal ganglia, it is apparent that over the whole of either the feeding group or the enema group no marked difference in the pattern of segmental involvement can be

seen. But there is a difference of frequency between the two groups. The findings suggest that the virus may have to move along the length of the small intestine into the large intestine before passing the intestinal barrier and coming into effective contact with nerve cells. They also suggest that the virus may be, to some degree, altered or destroyed while resident in the stomach or small bowel.

Table III gives a comparison of the total number of lesions found in both groups of experimental animals and in the controls. The differences found in tenth and fifth nerve ganglia, while they are suggestive, are not statistically significant. On the other hand, a comparison of the percentage involvement of either the enema group or the feeding group with that of the controls demonstrates differences that are statistically significant.

Summary

A count was made of all focal inflammatory lesions found in the vagal, gasserian, and intervertebral ganglia of a series of 14 monkeys to which poliomyelitis virus had been administered either by stomach tube or by rectal tube, and of those found in 8 monkeys not exposed to the virus. The difference in the percentages of intervertebral ganglia involved when test animals are compared with controls is statistically significant: 12 per cent in 6 animals fed by stomach tube; 16 per cent in 8 animals to which virus was administered by rectal tube; and 2 per cent in the control group of 8 animals.

Similar lesions were not found in the central nervous systems of the animals examined.

The distribution of focal lesions in the intervertebral ganglia follows a pattern throughout the test series. Lesions were strikingly more numerous in the lower cervical and lumbosacral groups of ganglia.

A comparison of the lesions in the intervertebral ganglia of monkeys given the virus by stomach tube with those in monkeys given the virus by rectum shows no difference in pattern, but the frequency of lesions in the former is suggestively less than that in the latter.

Treatment of virus suspensions with Duponol did not seem to increase the numbers of lesions found in sensory ganglia.

An attempt to facilitate the passage of virus from the intestinal lumen to the nervous system by administration of histamine dihydrochloride gave inconclusive results.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

The plates are arranged so that lesions of similar severity in test and control animals may be readily compared. It should be noted that none of the lesions is extensive; those shown include the most severe, together with some less severe. Sections from control animals cover almost all the lesions found in that series.

Sections on the left in each plate are from sensory ganglia of monkeys exposed to the virus of poliomyelitis; those on the right are from monkeys that had no known exposure to the virus. Figure 15 shows a spinal ganglion from a monkey that had severe poliomyelitis with marked lesions of the spinal cord, and that was sacrificed during the acute stage of the disease. While the cellular reaction is not wholly similar to that shown in the other figures, it can be seen that the process involves the destruction of single neurons; in other words, that the total picture consists of many individual foci, any one of which may be compared with a focus in an experimental animal.

Tissues were fixed in 70 per cent alcohol, cut in paraffin, stained with thionin, differentiated in alcohol.

PLATE 76

FIG. 1. Monkey 322. Right 7th cervical ganglion. Virus administered by enema. Sacrificed on the 17th day. Figures 1 to 4 represent the more marked type of lesion found in test animals and show loss of one or more neurons, with fairly dense inflammatory reactions. × 125.

FIG. 2. Monkey 328. Right 1st sacral ganglion. Virus by enema. Sacrificed on the 21st day. Section represents the severe lesion. × 125.

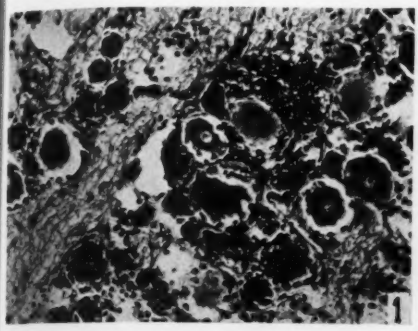
FIG. 3. Monkey 277. Gasserian ganglion. Virus by enema. Sacrificed on the 12th day. Section represents the severe lesion. × 125.

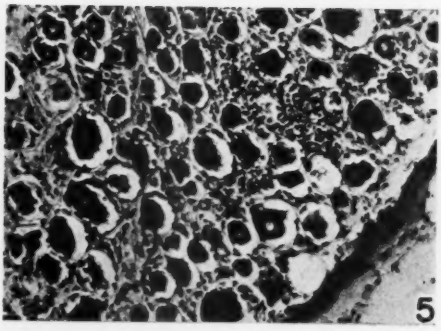
FIG. 4. Monkey 328. Left 2nd sacral ganglion. Virus by enema. Sacrificed on the 21st day. Section represents the severe lesion. × 125.

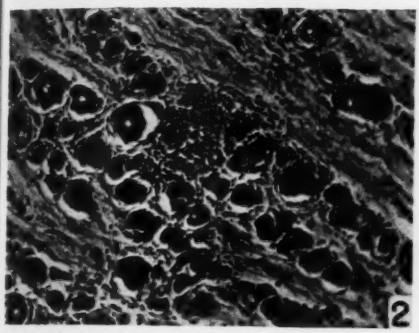
FIG. 5. Monkey 394. Left 2nd lumbar ganglion. No virus. The animal was emaciated and was sacrificed; no specific disease was identified. Figures 5 to 8 represent more definite lesions in the control series. × 125.

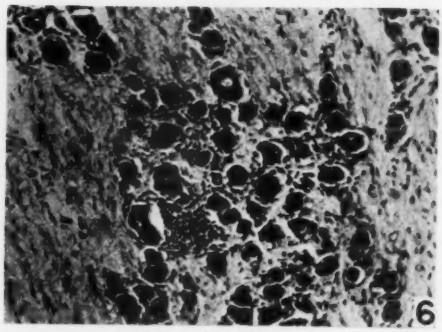
FIG. 6. Monkey 392. Left 2nd dorsal ganglion. No virus. When sacrificed, the animal exhibited extensive tuberculosis. Section represents more definite lesion in the control series. × 125.

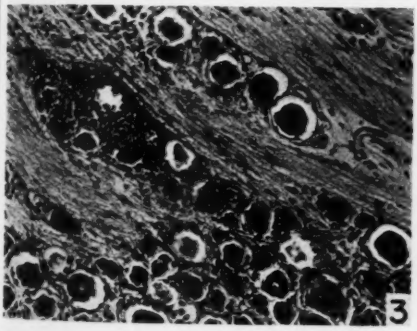
FIGS. 7 and 8. Monkey 293. Figure 7: Vagal ganglion. Figure 8: Right 8th cervical ganglion. No virus. Animal died spontaneously; pneumonia was found at autopsy. Sections represent more definite lesions in the control series. × 125.

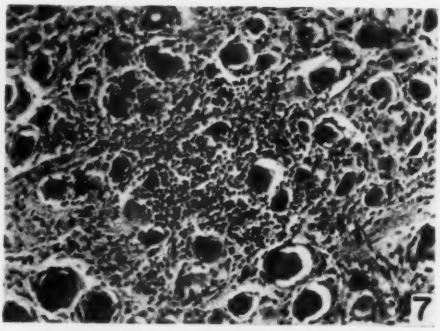


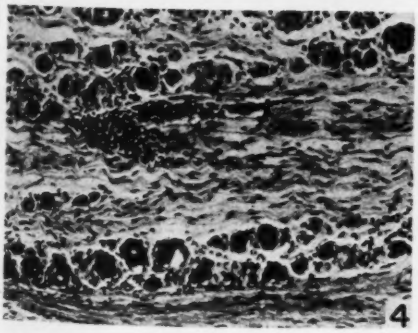


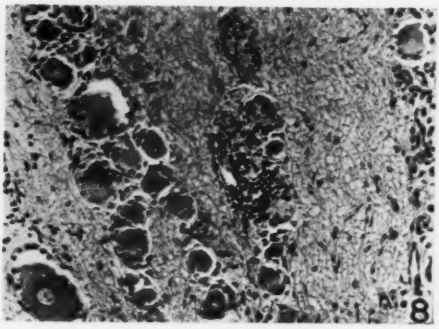












McClure

Sensory Ganglia in *Macaca mulatta*

PLATE 77

FIGS. 9 and 10. Monkey 322. (See also Fig. 1.) Figure 9: Vagal ganglion. Figure 10: Left 2nd sacral ganglion. Virus administered by enema. Sacrificed on the 17th day. Figures 9 to 11 represent less severe lesions found in test animals. × 125.

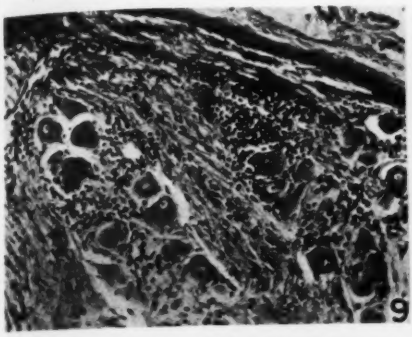
FIG. 11. Monkey 277. (See also Fig. 3.) Right 4th lumbar ganglion. Virus by enema. Sacrificed on the 12th day. Section shows less severe lesion found in test animals. × 125.

FIG. 12. Monkey 391. Vagal ganglion. No virus was administered, but animal was sickly. It was sacrificed but no specific disease was found. Section shows less severe lesions found in control animals. × 125.

FIG. 13. Monkey 392. (See also Fig. 6.) Gasserian ganglion. No virus. When sacrificed, animal exhibited extensive tuberculosis. Section shows less severe lesion found in control animals. × 125.

FIG. 14. Monkey 394. (See also Fig. 5.) Left 5th lumbar ganglion. No virus. The animal was emaciated and was sacrificed; no specific disease was identified. Section shows less severe lesions found in control animals. × 125.

FIG. 15. Intervertebral ganglion. Animal had severe poliomyelitis involving the spinal cord. It was sacrificed during the acute stage of the disease. × 125.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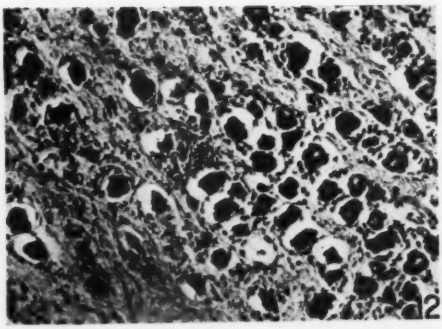
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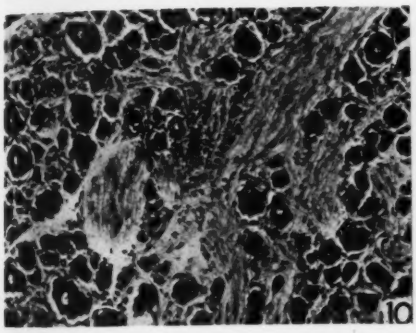
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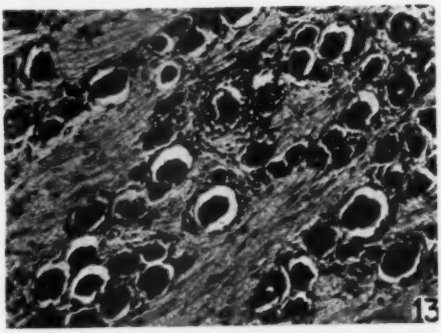
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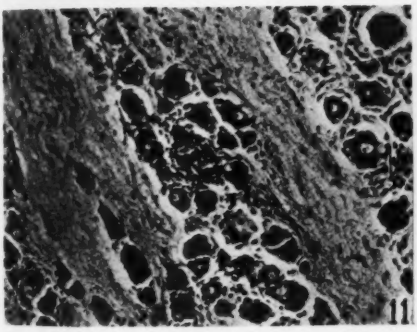
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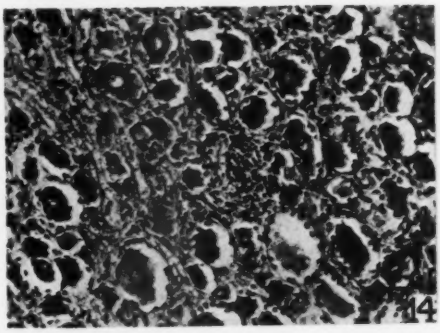
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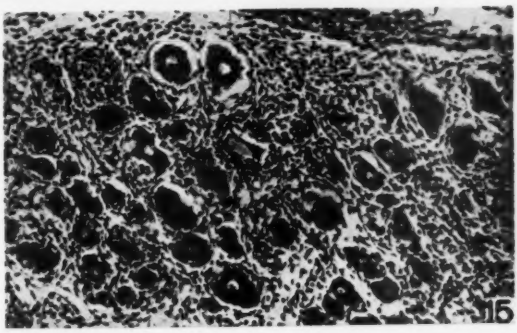
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THE PATHOLOGY OF CONVALESCENT POLIOMYELITIS IN MAN *

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The description of the pathology of poliomyelitis, like that of most acute and self-limited diseases, has been restricted almost entirely to the conditions obtaining at the climax of the illness. Death, when it occurs, may either result early from an overwhelming infection, or more commonly from respiratory failure at the crisis on or about the fifth day. Practically, these are the patients which the pathologist gets the opportunity to examine. Those who survive the crisis as a rule recover, though with a varying degree of residual paralysis. Relapse or a second attack is exceedingly rare. Such survivors often live out the usual span of life, and the few who have come to autopsy years after their illness show, as expected, only patches of atrophy and sclerosis to mark those areas most severely damaged in the acute illness.

Attempts to obtain information on the pathology of the convalescent stage of poliomyelitis indirectly through animal experimentation are also subject to severe limitation. In part this is due to the fact that certain species of monkeys are still the only animals known to be susceptible to the general run of poliomyelitis virus. A more serious obstacle to the experimental investigation is the circumstance that poliomyelitis is a much more highly fatal disease in monkeys than it is in man. It is relatively easy to produce poliomyelitis in monkeys by inoculation with any of the laboratory-adapted strains of virus, but the great majority of infected animals die at the height of their illness in spite of nursing care. For this reason a large number of animals must be lost in order to obtain a few in the convalescent stage. The considerable expense and labor required has apparently prevented the carrying out of any planned experiment along these lines. However, from the accumulated material of the Rockefeller Institute, Warburg [1] obtained the brains of 15 monkeys which had lived from 19 to 309 days after inoculation. From these she prepared a detailed description of the histology of the stage of repair of poliomyelitis in the monkey.

The introduction of the mechanical respirator about 13 years ago, and its subsequent increasingly widespread use, might have been expected to provide some human subjects for the study of the pathology of convalescent poliomyelitis. However, few, if any, studies of that

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character have been published. Probably the reason is that the respirator does not alter the basic nature of the poliomyelitic process. Artificial respiration is generally unable to prolong, to any degree, the life of the patient with severe bulbar involvement. On the other hand, many patients with paralysis of the muscles of respiration, saved by the respirator during their acute illness, later recover sufficient functional power to become more or less independent of the respirator. Such patients pass through convalescence to the stage of permanent arrest and scarring, and may live many years thereafter. Only occasionally is the balance between life and death so delicately poised that some small accident can upset it and cause the death of the patient during the early convalescent period. The three cases to be described are among the very few of this sort that have come to autopsy.

Reports of Cases

The three subjects of this report were victims of the 1941 outbreak of poliomyelitis in Tennessee. Two had been patients at the Vanderbilt University Hospital. The third was examined at the Erlanger Hospital, Chattanooga. They survived 7, 15, and 18½ weeks respectively from the onset of their acute illness. The important features of the clinical course of each are presented in the following summary.

Case 1 (7 Weeks' Survival)

The illness of this white girl, 3 years of age, began with fever, vomiting, and pain in the stomach. This was soon followed by tenderness and rigidity of the neck, increasing weakness of the legs and rapid respiration. She was brought to the hospital on the third day. Examination on admission showed complete flaccid paralysis of both legs, marked weakness of the arms, more on the left, and apparently complete paralysis of the right chest and diaphragm. Function of the cranial nerves appeared normal. She was immediately placed in a Drinker respirator where she remained almost constantly for 3 weeks. After her acute illness subsided, she was able to remain outside the respirator for increasing intervals up to 1 hour. Fluoroscopy during this time revealed paralysis and paradoxic movement of the right diaphragm. While convalescing in the hospital she contracted a mild respiratory infection and responded poorly to treatment. Administration of oxygen and attempted aspiration failed to relieve her respiratory distress and she died 50 days after she was stricken with acute poliomyelitis.

Case 2 (15 Weeks' Survival)

This white girl, 4 years old, entered the hospital acutely ill, extensively paralyzed, and breathing and swallowing with difficulty. Examination on admission showed that only a few weak movements could be made by the arms and legs. The intercostal muscles seemed completely paralyzed and respiration was effected by means of accessory muscles and the diaphragm. She remained in the respirator constantly for 3 weeks during which the acute illness subsided. Following this she gradually became able to leave the respirator, and after 5 weeks was discharged to a convalescent home for physiotherapy and rehabilitation. There she remained 10 weeks

till her final illness. During this time there was little improvement in muscle function. The intercostal muscles were nearly totally paralyzed and breathing was entirely diaphragmatic. Muscles of the extremities were flaccid and atrophic and still showed some tenderness. In the arms, flexion of the fingers and flexion and extension of the wrists were the only active movements possible. Motion in the legs consisted of abduction of the left thigh, and very weak movements of most of the muscles of the right leg. The Babinski sign could be elicited on both sides. As in case 1, this patient contracted a cold which she tolerated poorly because of her impaired respiratory musculature. As her condition became worse, she was placed briefly in a respirator, but she was not helped by it as she seemed unable to accommodate her breathing to the rhythm of the machine. Bronchopneumonia developed, and in spite of the administration of oxygen, sulfathiazole, and a blood transfusion she died on the sixth day of her illness, 106 days after being stricken by poliomyelitis.

Case 3 (18½ Weeks' Survival)

This white boy, 14 years old, was admitted to the hospital on the third day of his illness. At that time he presented incomplete paralysis of both upper and lower extremities. Because of respiratory distress he was placed in a respirator. His acute illness subsided, but he never regained sufficient function of his respiratory musculature to remain for long outside the respirator. After 4 months, however, he had improved sufficiently to be sent home for the Christmas holidays in a respirator. While at home he suddenly had six generalized convulsions within a few hours. He was immediately returned to the hospital, where he died within 24 hours after admission and 130 days after he was first stricken with poliomyelitis.

Material and Methods

Complete autopsies were performed on cases 1 and 2. The brain, the entire spinal cord with most of the thoracic and lumbar root ganglia, the sympathetic chains and the gasserian and celiac ganglia were removed from both and fixed in formaldehyde. From case 3 only the brain and the viscera were obtained for study. Blocks from all three specimens were cut according to a uniform scheme being employed at the National Institute of Health for the investigation of acute poliomyelitis. This, in brief, consisted of cutting large blocks from transverse slices through 30 planes. By this means some 95 blocks were prepared representing fairly completely most of the important structures from the frontal cortex to the caudal end of the medulla. Ten transverse sections were made at representative levels from each spinal cord. The sensory, gasserian, and sympathetic ganglia were cut to obtain the largest surface. All blocks were hardened for 4 days in 2½ per cent aqueous potassium bichromate, embedded in paraffin and sections cut at 8μ. For the general survey a complete set of sections was stained with eosin and methylene blue and thoroughly examined with the aid of a mechanical stage. Glial scarring in selected sections was stained by a modification [2] of Mallory's phosphotungstic acid hematoxylin method, suitable for tissues fixed in formaldehyde. Alterations in myelin sheaths were demonstrated in celloidin sections of selected

levels of the spinal cord stained by the Weigert-Pal technic. Frozen sections of suitable regions were stained for fat with Sudan IV, and for neuroglia and neurofibrils by various silver impregnation methods.

Gross Pathology

Gross examination of the fixed brain specimens during preparation of blocks for section revealed nothing more than some questionable paling of the substantia nigra. Cell loss, chiefly in the medulla, was too subtle to be grossly apparent and alterations in consistence due to gliosis were not perceptible in the hardened tissues. In the anterior horns of the cord, however, there were asymmetric brownish stains extending through a variable number of segments. Such discoloration was probably caused by congested and perhaps numerically increased vessels shining through tissue made more translucent by the loss of ground substance and finer myelinated fibers. At this early stage of repair there was very little gross shrinkage of the anterior horns. Instead, in the most severely damaged lumbar segments, the anterior horns had a loose and very delicate spongy texture, seeming to be almost cystic in some sections.

Microscopic Pathology

Cerebral Cortex. Lesions attributable to poliomyelitis were found only in the cortex of the paracentral lobule. In all cases there were one or two small focal accumulations of hypertrophied astrocytes and microglia located principally in the Betz cell layer (Fig. 1). Such scars were chiefly cellular, and only a few neuroglial fibrils were produced. In all cases there seemed to be some diminution of the total number of Betz cells, but the degree of loss was difficult to estimate. Small collars of lymphoid cells were also present about occasional vessels in the cortex of the paracentral regions. Throughout the subcortical white matter, but especially in that beneath the precentral gyri, there were occasional perivascular accumulations of macrophages filled with fat globules or masses of greenish brown, iron-containing pigment.

In case 3 such lesions were overshadowed by the recent thrombosis of a number of small vessels in the cortex at the dorsal end of the central gyri, and the consequent recent infarction of patches of the gray matter. Microscopically this vascular occlusion appeared to have been of very short duration, and quite likely it provided the irritative focus that touched off the patient's generalized convulsions. No anatomic cause for the thrombosis was demonstrable in the sections examined. There was also recent necrosis, without reaction, of Sommers' sector over a considerable length of the left hippocampus. Such a

lesion is occasionally found after convulsive attacks, and now is commonly regarded as a result rather than the cause of the seizures.

No lesions attributable to poliomyelitis were observed in the olfactory bulbs, tracts and trigones or in the hippocampi of any of the three specimens.

Basal Ganglia and Thalami. Even during the height of the acute disease process it is very rare to find more than scanty round cell infiltration about an occasional vessel in the caudate and amygdaloid nuclei, putamen, and claustrum. In the convalescent stage only a few lymphocytes and monocytes, some containing pigment, are to be seen about one or two large veins traversing these nuclei.

The more susceptible globus pallidus and thalamus which regularly show considerable damage in the acute stage, correspondingly present some residual inflammatory changes during convalescence. Their number and character seem to be determined at least partly by the time elapsed since the acute illness. In case 1 after 7 weeks, mild perivascular infiltration and a few loose patches of microglial proliferation were still to be seen in the globus pallidus and thalamus, chiefly along the lateral and ventral margins. In the older cases 2 and 3 cellular reaction in the parenchyma had subsided, and only occasional small perivascular collars of lymphoid cells remained. In all three specimens there were scanty infiltrations of lymphoid cells about some vessels traversing the hypothalamus and anterior perforated substance.

Midbrain. Marked residual inflammatory changes were still present in the midbrain of the first patient 7 weeks after the acute illness. The greatest damage was found in the substantia nigra. Here on both sides there were asymmetric patches in which the ground substance was loose and spongy. In the largest of these, nerve cells had nearly all disappeared, and there was an abscess-like accumulation of foam cells. Nearby vessels were surrounded by broad collars (Fig. 2), while vessels more distant and those traversing the peduncles were occasionally surrounded by mantles of lymphoid cells. In the center of one such foam cell "abscess" was a large multinucleated giant cell of the foreign body type, probably a response to the disintegration products of lipoid material. Rarely at the edges of these foci there were coagulated and granular bodies of nerve cells surrounded by phagocytic microglia. Scattered outside the margin were a moderate number of hypertrophied astrocytes. In addition to such areas of destruction there were a few small, focal microglioses in the substantia nigra.

Other structures at the same level presented less severe lesions. In the red nuclei there were a few prominent perivascular collars of lymphoid cells, and occasional small microglial foci and hypertrophied

astrocytes. A very small group of mixed microglia and astrocytes was still evident in the middle and deep layers of anterior colliculi. Two small microglial foci, one surrounding an apparently intact nerve cell, were present in the left oculomotor nucleus.

In cases 2 and 3 of about 4 months' duration the residual inflammatory reaction was much less marked, though of course there is no certainty that damage during the acute illness was equally severe. Both showed occasional collars of lymphoid cells about vessels in the peduncles, substantia nigra and red nuclei. A few small patches of microglial proliferation were present, chiefly near the margin of the red nuclei, and rarely in the substantia nigra and anterior colliculi.

At the level of the posterior colliculi all three cases were practically identical in presenting only mild inflammatory reactions and neuroglial scarring. The chief damage appeared in the lateral tegmental nuclei and caudal end of the substantia nigra. There had been some loss of nerve cells from these structures, and the ground substance contained a moderate number of microglia and scattered hypertrophied fibrous astrocytes. Mild round cell infiltration was present about some of the vessels in these nuclei and in the median raphe. In case 3 only, there were single, small microglial stars in the periaqueductal gray matter and in the left posterior colliculus.

Pons. Three complete transverse sections were made of the pons, one through the anterior medullary velum, one at the level of the trigeminal roots, and one through the abducens nuclei. In all three cases a considerable amount of residual inflammatory reaction persisted in the tegmentum, and as expected the lesions were most marked and acute in character in the case of shortest duration.

At the level of the anterior medullary velum, sections from case 1 showed moderate loss of cells bilaterally in the locus coeruleus, and in their place a considerable proliferation of microglia and foam cells. A similar though less abundant microgliosis was present in the nearby lateral tegmental nuclei. Scattered hypertrophied astrocytes were seen in these lesions, chiefly in the periphery, and a loose irregular patch of microglia and astrocytes appeared in the ventricular floor on the left. Small collars of lymphocytes mixed with some foam cells surrounded a number of vessels in the tegmentum. In sections at this level from the two older cases most of the cellular reaction had subsided, leaving behind scattered hypertrophied astrocytes in the reticular substance, a few small microglial stars, and scanty round-cell infiltration about the regional vessels.

In sections through the trigeminal roots the most obvious lesions were found in the motor nuclei of the V nerve, and unexpectedly they

seemed to be most active in case 3 which had survived 4½ months. In this specimen the lateral half of the right motor V nucleus presented considerable focal and diffuse microgliosis. Several large nerve cells were coagulated and being attacked and removed by phagocytic monocytes (Fig. 3). A few nearby vessels were surrounded by broad collars of foamy and lightly pigmented cells. Among nerve cells at the margin of this lesion were scattered hypertrophied astrocytes (Fig. 4). Some nerve cells had been lost from the motor V nuclei of case 2 and their places were occupied by microglia and a few large fibrous astrocytes. The motor V nuclei of case 1 were apparently intact.

In all three specimens there were scattered, rather prominent perivascular collars in the ventricular floor and reticular substance. Some of the large nerve cells had disappeared, and there was a mild increase of microglia and scattered hypertrophied fibrous astrocytes throughout the reticular substance. No necrotic cells remained but in case 1 a few apparently intact large nerve cells were surrounded by small groups of microglia. No lesions were found in the sensory V nuclei of any of the specimens.

Sections of the posterior part of the pons through the level of the abducens nuclei presented in all three specimens about the maximum degree of destruction of the nervous parenchyma observed throughout the entire brain stem. The most severe damage regularly appeared in the lateral vestibular nuclei of Deiters. The loss of nerve cells was greatest—about 75 per cent bilaterally—in case 1, somewhat less and chiefly on the right side in case 2, and still less in case 3. Corresponding to the cell loss, the nuclei appeared as a somewhat shrunken spongy network of coarse glial fibers and hypertrophied astrocytes (Fig. 5), in the meshes of which were a considerable number of microglia and some foam cells. In case 1 at 7 weeks a few spherical, coagulated masses, apparently dead cell bodies, were embedded in the inflammatory tissue; and a single similar dead cell, without apparent reaction, was still present in Deiters' nucleus of case 3, 4½ months after the onset of poliomyelitis (Fig. 6). Some loss of cells and neuroglial reaction extended irregularly into the adjacent portions of the medial and superior vestibular nuclei. Prominent collars of lymphoid cells surrounded a number of vessels traversing these nuclei.

Damage was present but less severe in the other nuclear masses at this level. As in preceding sections there had been some loss of individual large cells in the reticular substance, and in their places were occasional hypertrophied astrocytes or small groups of microglia. In case 1 only, there was a single abscess-like focus of foam cells surrounded by hypertrophied astrocytes in the ventral part of the right

side (Fig. 7). All three cases presented, on one side or the other, loss of a few cells in the facial nucleus, and in their place some proliferation of microglia and astrocytes. In all there were small collars of lymphoid cells about occasional vessels in the tegmentum. No definite parenchymatous lesions were observed in the abducens and descending V nuclei, or in the superior olives and the gray matter of the basal pons in any of the three specimens.

Cerebellum. Three transverse blocks were cut from the cerebellum of each specimen; one through the anterior medullary velum, one through the center, and one through the caudal third of the hemispheres. Residual inflammatory reaction and scar formation in the cerebellum followed closely the usual pattern of the acute disease. The most evident damage was seen in the tectal nuclei. In all three cases there appeared to have been some loss of nerve cells. The ground substance was loose and spongy and contained an increased number of microglia, some rod cells and a few hypertrophied astrocytes. Regional vessels were surrounded by small collars of lymphoid cells. No parenchymatous lesions were present in the dentate nuclei, but there was a scanty round-cell infiltration about occasional vessels in the hilum. Changes in the cerebellar cortex were strictly limited to the molecular layer of the vermis. Such lesions appeared as irregular vertical streaks of astrocytes and a few microglia crossing the molecular layer. The ground substance was partly dissolved, and among the cells were a moderate number of coarse neuroglia fibrils. Often there was a patch of round-cell infiltration in the overlying meninges (Fig. 8). A few single lesions of this type were present in the first two cases, but none was observed in case 3.

Medulla. Transverse sections were made of the medulla through the VIII nerve roots, at the midpoint of the inferior olives, through the point of closure of the fourth ventricle, and through the decussation of the pyramids.

Lesions at the level of the VIII nerve roots were in general a continuation of those already described in the caudal edge of the pons. Included portions of the VII and lateral vestibular nuclei showed some asymmetric loss of cells and corresponding patchy gliosis. Damage in the reticular substance appeared to be maximal at this level. In case 1 part of the ground substance had disappeared in an abscess-like patch of foam cells. No actual solution of ground substance appeared in cases 2 and 3, but the framework was spongy, somewhat collapsed and contained scattered hypertrophied fibrous astrocytes and small groups of microglia. A number of the large nerve cells had disappeared, and in both cases 2 and 3 there were still single coagulated cells undergoing

neuronophagia 4 months after the acute illness (Fig. 9). It is noteworthy that maximum lesions in the reticular substance appeared in this level, comprising the middle reticular nuclei which had connections with the severely damaged vestibular nuclei and with the anterior horns of the cord. Moderate perivascular infiltration appeared in the affected areas. In the medial vestibular and spinal V nuclei, and rarely in the white matter of the restiform bodies, small microglial stars were to be seen. No lesions were present in the cochlear nuclei.

The middle half of the medulla, as represented by sections through the olives and the closure of the ventricle, presented comparatively mild focal lesions distributed rather irregularly in the dorsal part. In all specimens there was scanty perivascular infiltration, a few small groups of microglia, and scattered astrocytes in the reticular substance and ambiguus nuclei. Little if any loss of nerve cells was demonstrable. One or two cuffed vessels and a few small glial stars were present irregularly in the hypoglossal and lateral cuneate nuclei. In cases 2 and 3 small hemorrhages appeared in the dorsal motor vagus nuclei. Apparently these occurred shortly before death, as there was no reaction to the effused blood, and no visible changes in the adjacent tissue. No lesions were found in any case in the nuclei of the tractus solitarius, the spinal V nuclei, and the inferior olives.

At the level of the decussation of the pyramids the distribution of lesions became practically identical with that in the spinal cord. Damage was chiefly in the anterior horns, where nearly three-fourths of the nerve cells had disappeared, though characteristically the loss was not symmetric. The horns had collapsed somewhat, and the ground substance contained a moderate number of mononuclear (microglial) inflammatory cells. Mingled with them but more numerous along the margins of the horns were a number of hypertrophied astrocytes producing a quantity of coarse glial fibrils. Such fibrous gliosis was more marked in the two later cases (Fig. 10). Prominent collars of lymphoid cells mingled with some fat-laden macrophages surrounded a number of vessels in the anterior horns and central gray matter. There was a mild diffuse hyperplasia of astrocytes in the ventral and lateral white matter surrounding the anterior horns. This appearance was most marked in case 2, in which this portion of the white matter had a coarse, loose texture as if there had been some loss of individual myelin sheaths. In case 1 alone, single small foci of microglia and some astrocytes were present in the nuclei gracilis and cuneatus, while in both cases 1 and 2 a few small glial stars were found in the white matter of the posterior columns. No lesions were present in the spinal V nuclei in any of the three specimens.

Spinal Cord. The entire spinal cord was obtained from cases 1 and 2, but only the first cervical segment was available from case 3. Ten blocks, three each from the cervical, thoracic and lumbar regions and one from the conus medullaris, were cut from each specimen. These were supplanted by other representative blocks taken for special staining methods. As might be anticipated from the extent and severity of the paralysis, both spinal cords presented extensive destruction throughout their entire length. The various levels differed so little in the degree of damage that the spinal cord is best described as a unit.

Loss of the large nerve cells of the anterior horns was almost complete in both cases save at the extreme caudal end of the cord. The few surviving nerve cells were nearly all found along the medial and ventral margins of the anterior horns in the region generally considered to innervate the trunk musculature. In case 1 a few coagulated nerve cell bodies were still to be seen in the lumbar enlargement after 7 weeks (Fig. 11), but in case 2 at 15 weeks the removal of dead cells was practically complete and only rare shrunken masses of uncertain nature remained in the lower lumbar cord.

Damage and loss of nerve cells in the lateral horns appeared to have been initially greater in case 1. In it almost all cells had disappeared from one or the other side in some midthoracic segments. For the most part, however, both cases showed a partial loss of nerve cells in a patchy and asymmetric pattern. Often the disappearance of a few nerve cells was most clearly indicated by the presence of several hypertrophied fibrous astrocytes which filled the gap in the tissue (Fig. 12).

Lesions in Clarke's column appeared only in case 1. Because of the normal irregularity of this structure, the degree of cell loss was difficult to estimate. However, throughout its length there was evidently some patchy disappearance of nerve cells, and in their places were small groups of hypertrophied fibrous astrocytes, as were also seen in the lateral columns. In the transitional zone between thoracic and lumbar regions there was nearly complete destruction of Clarke's columns on both sides. Practically all nerve cells had been removed, and the columns appeared as loose reticular patches of glial fibers containing a number of mononuclear and foam cells as well as large fibrous astrocytes (Fig. 13).

Involvement of the posterior horns evidently resulted secondarily by spreading of the inflammatory process from the anterior horns. Gliosis was most pronounced along the border of the anterior horns in the cervical and lumbar enlargements, and diminished toward the posterior roots. Save for an occasional hypertrophied astrocyte along the root filaments, no definite lesions appeared in the substantia gelatinosa.

Changes in the interstitial tissue of the spinal gray matter were determined by the degree of neuronal damage and by the length of time elapsed since the acute illness. Where only a few cells were destroyed, as in the lateral horns, the ground substance partly collapsed, and nearby astrocytes enlarged and produced a small tangle of coarse glial fibrils. In areas of massive inflammation and destruction of many neurons in the anterior horns, most of the neuropil and fine medullated fibers had disappeared, and their place was taken by a meshwork of glial fibrils. In case 1 at 7 weeks this network was delicate and silky and showed little contraction. The astrocytes laying down the fibrils were bulky with abundant cytoplasm, and were numerous around the margin (Fig. 14). Lying among the glial fibrils were still a moderate number of mononuclear and foam cells containing lipoid débris. Capillary vessels were prominent, though their increase may have been only apparent, and many were surrounded by broad collars of lymphoid and foam cells. In case 2 at 15 weeks the feltwork of glial scar had become more dense, but shrinkage of the anterior horns was only moderate. The glial fibrils were considerably more coarse, and the astrocytes had lost much of their bulky cytoplasm and appeared as dark-stained angular cells (Fig. 15). Scattered mononuclear inflammatory cells still remained. Removal of débris was nearly complete, and only in the cervical and lumbar enlargements where considerable tissue was destroyed were a few lipoid-filled foam cells to be seen. Vessels were less prominent, and perivascular infiltration scanty save for thick collars about a few single vessels.

Damage in the white matter of the spinal cord, as shown in myelin sheath preparations (Fig. 16), consisted of a partial but definite demyelinization due to a loss of individual fibers rather than interruption of an entire tract. As expected, it appeared more clearly in the older case 2. In the ventral and lateral columns there was some loss of fibers in all regions save the pyramidal tracts, but the paling was most clearly seen in the superficially placed spinocerebellar tracts. In the dorsal columns the demyelinization was more sharply limited to the fasciculus interfascicularis or comma tract of Schultze. Probably much of the fiber loss in the ventral ground bundles was the result of destruction of cells of origin in the anterior horns. However, the degeneration of the spinocerebellar and comma tracts cannot be explained satisfactorily on the basis of their presently accepted connections. Scarcely any cell loss was perceptible in the dorsal root ganglia and posterior horns, and though a number of cells had been destroyed in Clarke's column in case 1, demyelinization in the dorsal spinocerebellar tract seemed slightly less than in case 2 in which Clarke's column was almost intact.

Routinely stained sections showed a mild diffuse hyperplasia of astrocytes in the demyelinated areas, and there was probably a slight increase in size and number of glial fibrils.

Nerve Roots. The anterior nerve roots showed in striking manner the result of extensive destruction of motor nerve cells. In myelin sheath preparations (Fig. 17), more than 80 per cent of the myelinated fibers had disappeared. The loss of the coarse motor nerve fibers was nearly complete. Remaining fibers were, for the greater part, of small diameter with thin myelin sheaths, and most were probably the axons of efferent sympathetic neurons. This sparing of the sympathetic components of the anterior roots was especially striking in the thoracic segments where (Fig. 18), as was noted above, there was comparatively little diminution of nerve cells in the lateral horns.

Differences in the stage of nerve root degeneration due to the duration of the process may be observed in Weigert preparations, but are more clearly shown in ordinary stained sections. In the nerve roots from case 1 at 7 weeks there were still a number of phagocytes containing globules of lipoid material, some of which stained as myelin. In case 2 after 15 weeks no stainable globules remained, and the roots contained only the scattered surviving myelinated nerve fibers.

In routine sections of case 1 the anterior roots appeared moderately reduced in size and abnormally cellular. Under higher magnification (Fig. 19), the increased cellularity was seen to be due partly to proliferation of Schwann cells and endoneurial fibroblasts, but chiefly to accumulation of numerous foamy macrophages. These were arranged in bead-like rows, filling the endoneurial nerve tubes once occupied by large myelinated fibers. The phase of active proliferation of these cells was evidently passed since no mitotic figures were present.

The anterior roots of case 2 showed a more advanced stage of atrophy (Fig. 20). Their total size was greatly reduced. The endoneurial connective tissue seemed coarser and more abundant, though much of the apparent increase may have been due to collapse and shrinkage. Nerve tubes which had lost their fibers generally contained scattered Schwann cells. Some of the larger ones in cross section appeared quite empty. Only rarely were one or more foamy macrophages still to be seen. In both cases a scanty infiltration of lymphoid cells was found about a few of the small endoneurial blood vessels.

No significant lesions were found in the posterior nerve roots of either case.

Cerebrospinal Ganglia. Both gasserian ganglia and four representative pairs of dorsal root ganglia were examined from cases 1 and 2. In case 1 occasional small foci of lymphoid cells were still present after 7

weeks, in the stroma of both gasserian and root ganglia. Rarely in the lumbar ganglia a single nerve cell had disappeared, and its capsule was filled with proliferated satellite cells (Fig. 21). In case 2 after 15 weeks no lesions were found in the gasserian ganglia, and in the root ganglia there were only very rare small foci of lymphocytes.

Sympathetic Ganglia. Both thoracolumbar sympathetic chains and the celiac ganglia from both cases were examined. In each case the celiac ganglia contained a very few small foci of lymphoid cells, and in case 2 there were a few eosinophilic leukocytes among the bundles of nerve fibers. No lesions were found in the thoracolumbar sympathetic chains in either case.

Meninges and Choroid Plexus. Inflammatory reaction in the meninges was limited to a few scanty patches of lymphoid and mononuclear cells, not apparently related in any close fashion to lesions in the nervous parenchyma. In case 3 alone, the tips of the arachnoidal villi along the longitudinal fissure contained a moderate number of polymorphonuclear leukocytes. This unusual reaction was most probably a response to blood and irritative products of tissue disintegration seeping out from the patches of recent infarction in the paracentral lobules. No significant lesions were found in the choroid plexus of any of the specimens examined.

Attempt at Virus Isolation

A small piece of the cervical cord of case 3 was preserved in glycerine-saline solution to test for the presence of virus. Unfortunately the specimen was contaminated with bacteria not killed by the glycerine, and two monkeys inoculated intracerebrally died promptly of acute brain abscess, too early to show any possible evidence of poliomyelitis. Accordingly, the question of persistence of virus in the nervous system during convalescence remains unanswered. Since inflammatory reaction and a few necrotic cells are still found after 18½ weeks, it would appear desirable to do animal inoculations for virus whenever the rare opportunity is afforded of an autopsy on a patient in the convalescent stage of poliomyelitis.

Summary

The pathology of the residual lesions in three cases of poliomyelitis which had survived 7, 15 and 18½ weeks from onset of illness has been described and illustrated.

Lesions in the cerebral cortex consisting of perivascular collars of lymphoid cells and interstitial foci of microglia and astrocytes are confined to the paracentral lobules. Some diminution of Betz cells also

appears probable. In case 3, only, there was thrombosis of small vessels and patches of recent cortical infarction in the central convolutions at the vertex.

Only minimal lesions are found in the basal ganglia and thalami. In the earliest case, scanty perivascular infiltration and a few small microglial foci appear in the globus pallidus and ventral and lateral part of the thalamus. In the two later cases slight perivascular infiltration, only, is seen in these structures.

In the midbrain the substantia nigra presents the most severe damage. A few necrotic cells are still undergoing phagocytosis in case 1 at 7 weeks. Irregular perivascular infiltration, and interstitial foci of mixed astrocytes and microglia, appear in the lateral tegmental and red nuclei, generally in amount decreasing with the time elapsed since the initial illness.

Lesions in the pons are confined to the tegmentum. Loss of nerve cells is marked in Deiters' nuclei, and more patchy and asymmetric in the motor V and VII nuclei. Single necrotic cells are still present 4 months after the acute illness. Perivascular infiltration diminishes and the density of fibrous gliosis increases with the duration of convalescence. Part of the large nerve cells of the reticular substance have disappeared, leaving behind scattered large fibrous astrocytes. In case 1 part of the ground substance, as well as cells of the reticular substance, has been destroyed, leaving an abscess-like accumulation of foam cells.

In the cerebellum, lesions are found only in the tectal nuclei and in the cortex of the vermis. Some cells of the tectal nuclei have disappeared, and there is a patchy hyperplasia of astrocytes. In the vermis a few vertical streaks of astrocytes and microglia extend across the molecular layer of the cortex.

The most marked changes in the medulla consist of cell loss and scarring in the reticular substance similar to that found in the pons. Rare dead cells are still present in cases 2 and 3. Asymmetric glial patches are found in the ambiguus and hypoglossal nuclei. At the pyramidal decussation the lesions become practically the same as in the spinal cord. Only a few small glial stars appear in the nuclei gracilis and cuneatus and in their tracts.

The spinal cord presents an almost complete loss of nerve cells throughout the entire length of the anterior gray substance. In contrast the lateral horns are comparatively spared, lesions in Clarke's column are patchy and asymmetric, and no definite changes appear in the posterior horns. Replacement gliosis in the anterior horns is at first abundant but delicate, with bulky astrocytes. Later the cells

shrink and the fibrils become coarser. Numerous mononuclear inflammatory cells and rare necrotic nerve cells are still present in case 1, but have largely disappeared from the later cases.

In the white matter of the spinal cord there is a mild diffuse demyelinization of most of the ventral and lateral columns with the exception of the pyramidal tracts. In the posterior columns partial demyelinization is confined to the region of the comma tracts of Schultze. Much of this tract degeneration is due to factors other than loss of the known cells of origin.

The anterior nerve roots show severe degeneration consequent to the extensive loss of anterior horn cells. Almost all of the coarse motor fibers have disappeared. In contrast the fine myelinated efferent sympathetic fibers are mostly spared. At 7 weeks the nerve tubes contain many fat-laden phagocytes, but by 15 weeks nearly all phagocytes have disappeared, the roots are shrunken and the endoneurial connective tissue is somewhat increased. No changes are recognizable in the posterior roots.

In the gasserian, dorsal root and sympathetic ganglia there are a very few small foci of lymphoid cells. In the root ganglia only rare cells have disappeared, leaving behind capsules filled with mononuclear cells.

The meninges contain only a few scanty foci of lymphoid cells, and no lesions were found in the choroid plexus.

An attempt in case 3 to detect virus in a small portion of glycerinated spinal cord was frustrated by bacterial contamination of the inoculum.

Pathologic specimens and clinical data of cases 1 and 2 were furnished by Dr. G. John Buddingh, Department of Pathology, Vanderbilt University. Corresponding material of case 3 was contributed by Dr. Forrest G. Bratley, pathologist of the Erlanger Hospital, Chattanooga, Tennessee. The author is pleased to acknowledge his indebtedness to these pathologists whose generous donation of their specimens made possible this report.

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2. Peers, J. H. A modification of Mallory's phosphotungstic acid-hematoxylin stain for formaldehyde-fixed tissues. *Arch. Path.*, 1941, **32**, 446–449.

DESCRIPTION OF PLATES

PLATE 78

FIG. 1. Glial nodule in the motor cortex of case 1 (7 weeks). Eosin and methylene blue stain. × 155.

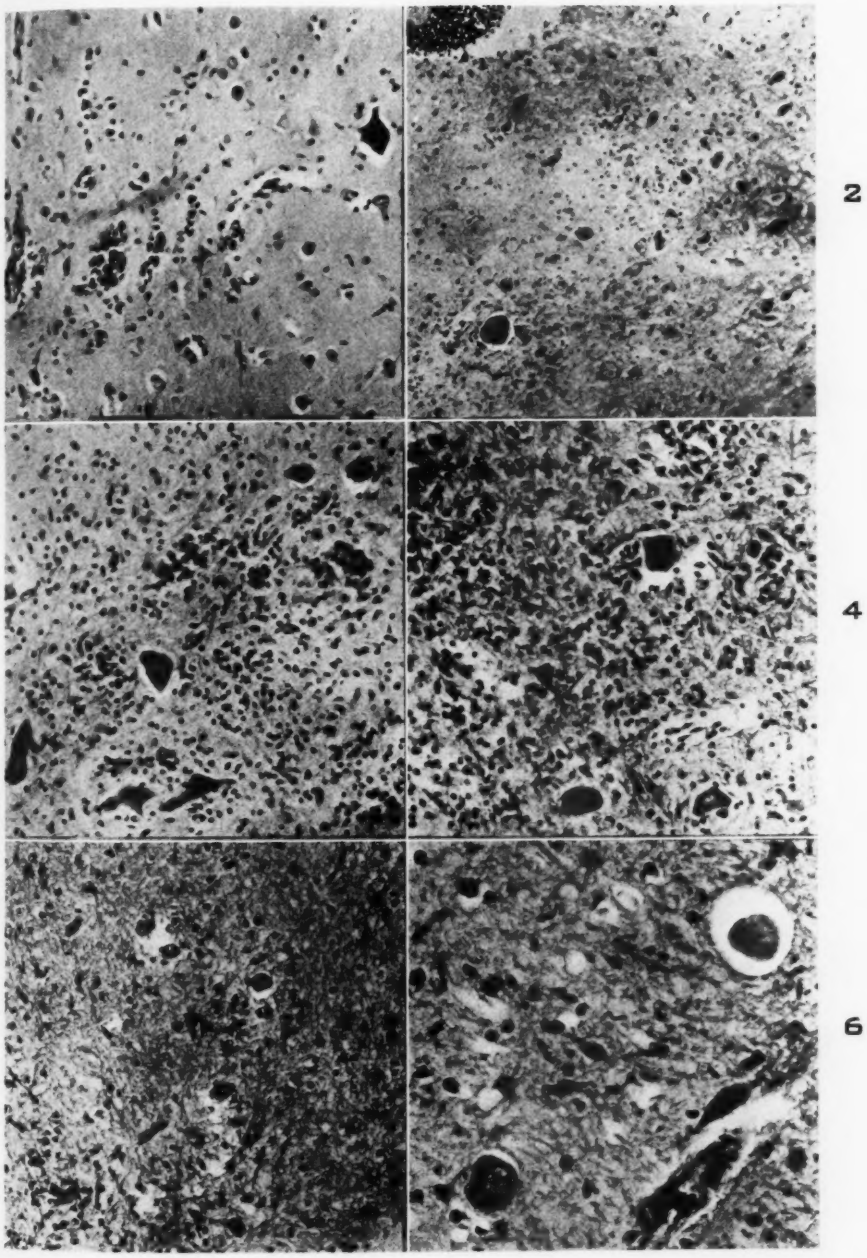
FIG. 2. Substantia nigra, case 1 (7 weeks), showing cell loss and foreign body giant cell. Eosin and methylene blue stain. × 105.

FIG. 3. Motor V nucleus of case 3 (18½ weeks), showing diffuse microglial infiltration and phagocytosis of a dead cell. Eosin and methylene blue stain. × 143.

FIG. 4. Same as in Figure 3 showing a few hypertrophied astrocytes and irregular feltwork of neuroglial fibrils. Phosphotungstic acid hematoxylin stain. × 183.

FIG. 5. Deiters' nucleus, case 2 (15 weeks), showing marked loss of nerve cells and collapsed and spongy ground substance with hypertrophy of astrocytes at the periphery. Phosphotungstic acid hematoxylin stain. × 143.

FIG. 6. Deiters' nucleus, case 3 (18½ weeks). A necrotic nerve cell without cellular reaction is seen in the upper right. Hypertrophy of astrocytes. Eosin and methylene blue stain. × 285.



Peers Convalescent Poliomyelitis in Man

PLATE 79

FIG. 7. Reticular substance of medulla, case 1 (7 weeks), showing diffuse microgliosis, loss of nerve cells and small foam cell "abscess." Eosin and methylene blue stain. × 80.

FIG. 8. Cerebellar cortex, case 3 (18½ weeks), showing vertical streak of microglia and astrocytes crossing the molecular layer. Eosin and methylene blue stain. × 155.

FIG. 9. Reticular substance of medulla, case 3 (18½ weeks), showing phagocytosis of a dead nerve cell and hypertrophy of surrounding astrocytes. Eosin and methylene blue stain. × 310.

FIG. 10. Upper cervical cord, case 3 (18½ weeks), showing hypertrophied fibrous astrocytes at margin of anterior horns. Phosphotungstic acid hematoxylin stain. × 143.

FIG. 11. Lumbar cord, case 1 (7 weeks), showing dead motor nerve cell, broad perivascular collar of foam cells and early gliosis in ground substance. Eosin and methylene blue stain. × 285.

FIG. 12. Thoracic cord, case 1 (7 weeks), showing hypertrophied astrocytes in the lateral horn. Phosphotungstic acid hematoxylin stain. × 285.

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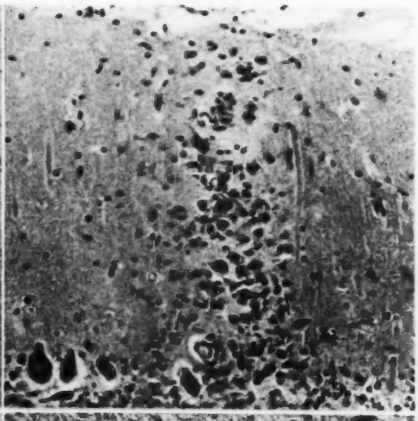

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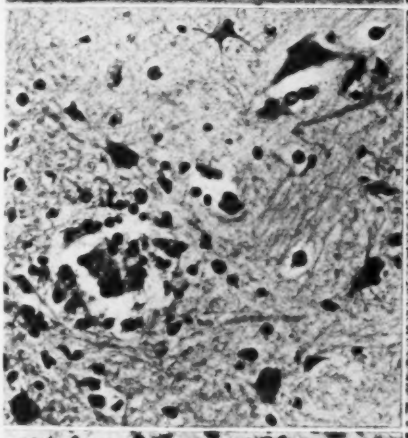

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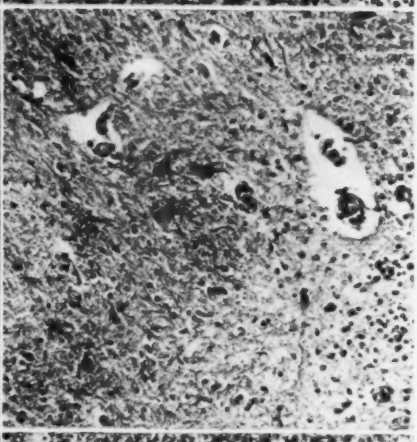

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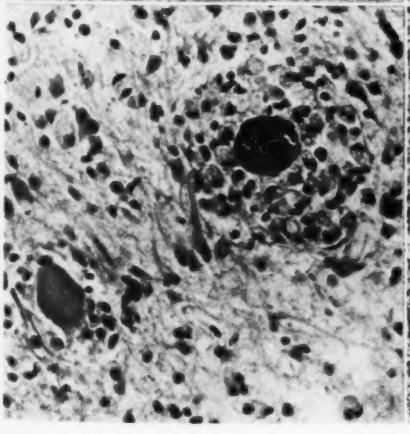

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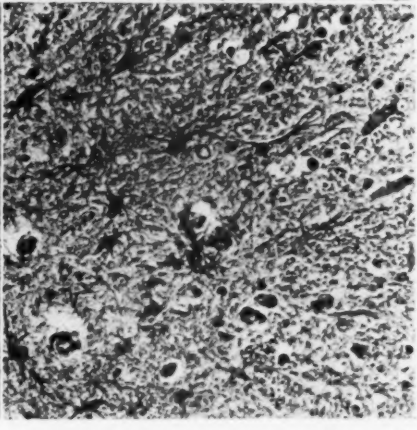

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Peers

Convalescent Poliomyelitis in Man

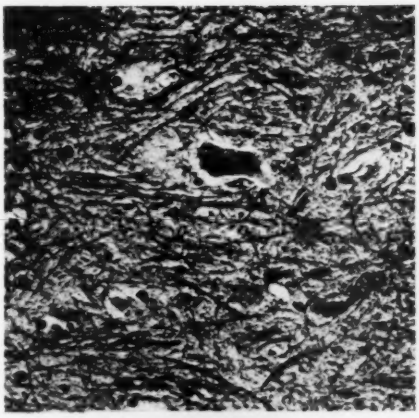
Plate 80

Fig. 13. Thoracic cord, Clarke's column, case 1 (7 weeks), showing microgliosis and hypertrophy of astrocytes. There is a dead cell body in the upper left portion of the figure. Phosphotungstic acid hematoxylin stain. × 285.

Fig. 14. Lumbar cord, anterior horn, case 1 (7 weeks), showing monocytes and foam cells in ground substance and about vessel; hypertrophy of astrocytes with sparse and irregular formation of neuroglial fibrils. Phosphotungstic acid hematoxylin stain. × 285.

Fig. 15. Lumbar cord, anterior horn, case 2 (15 weeks), showing abundant meshwork of coarse neuroglial fibrils and less bulky astrocytes. There are few remaining inflammatory cells. Phosphotungstic acid hematoxylin stain. × 285.

Fig. 16. Cross section of thoracic cord, case 2 (15 weeks), showing partial demyelinization of comma tracts, and of most of the medial and ventrolateral white columns. Weigert-Pal stain. × 10.



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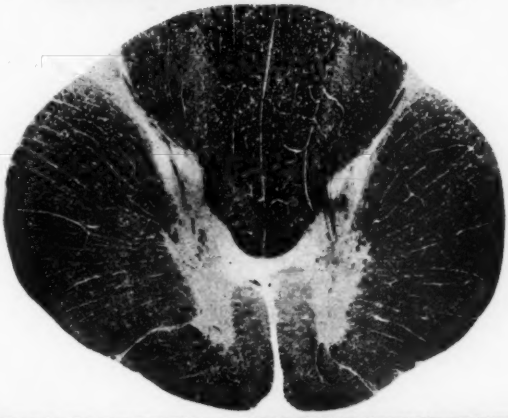

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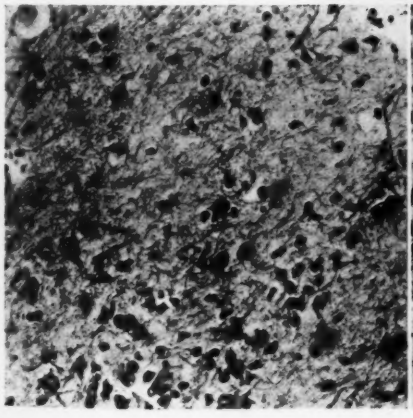

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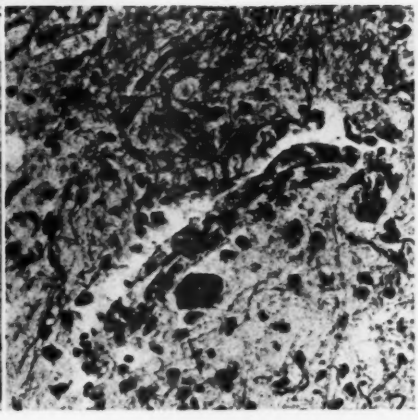

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Plate 81

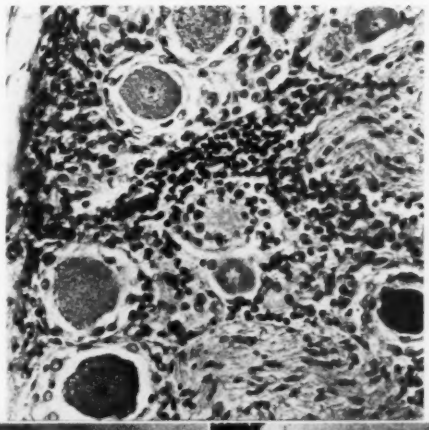
Fig 17. Anterior nerve root, lumbar region, case 2 (15 weeks), with loss of nearly all large myelinated nerve fibers. Weigert-Pal stain. × 75.

Fig. 18. Anterior nerve root, thoracic region, case 1 (7 weeks). There is nearly complete loss of large myelinated fibers. Fine medullated sympathetic fibers are practically intact. Weigert-Pal stain. × 75.

Fig. 19. Anterior nerve root, lumbar region, case 1 (7 weeks), showing fat-laden phagocytes occupying empty nerve tubes. Eosin and methylene blue stain. × 270.

Fig. 20. Anterior nerve root, lumbar region, case 2 (15 weeks), showing marked shrinking and some apparent increase of endoneurial connective tissue. Few reacting cells remain. Eosin and methylene blue stain. × 270.

Fig. 21. Dorsal root ganglion, lumbar region, case 1 (7 weeks), showing an interstitial focus of lymphocytic infiltration near the capsule. Eosin and methylene blue stain. × 235.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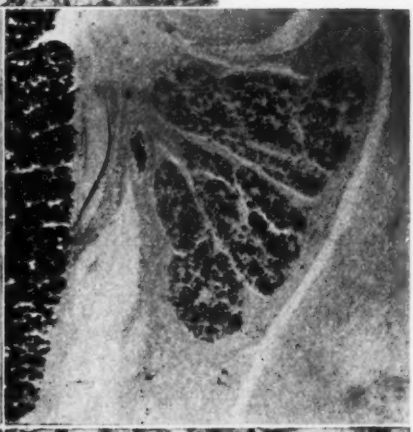
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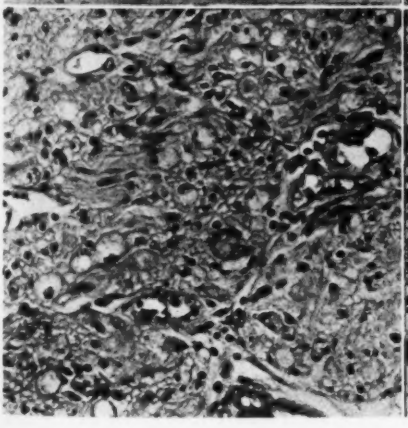
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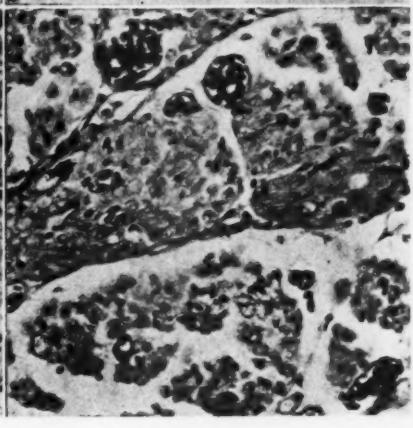
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ATROPHY OF THE BRAIN FOLLOWING PUERPERAL ECLAMPSIA *

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Mental deterioration following puerperal eclampsia is little known. Amand (1790), according to Sioli,[1] described a young woman who "lost her mental faculties to such an extent as to become unable to read and write and even monogram her linen, all things she had been able to do before." In modern literature there is only the clinical contribution by Nevermann,[2] who reported mild aphasia and moderate mental deterioration 5 years after childbirth complicated by eclampsia. We were unable to trace any patho-anatomic investigations on the subject and wish to present a case of advanced atrophy of the brain caused by this disorder.

REPORT OF CASE

Clinical History. A white married woman, 20 years of age, a primipara, gave birth to a child on March 21, 1930. According to the statement of the attending physician the pregnancy was uneventful until 3 days before delivery, when headaches occurred, the urine was found to contain large quantities of albumin and the blood pressure rose to 200/90 mm. of Hg. However, the delivery was rapid and uneventful, resulting in a living, normal child. One hour later there occurred almost continuous uncontrollable convulsive attacks which persisted for 14 hours. The patient remained comatose for 60 hours, regaining consciousness gradually. Ninety-six hours following delivery she opened her eyes, occasionally moved her extremities and swallowed liquids, but did not respond to questions, did not recognize relatives and did not talk. The pupils were enlarged (examination of the eyegrounds was not possible); the muscles were generally flaccid, but at times those of the neck and of the right arm were rigid and twitched spontaneously or on touch. All reflexes were exaggerated, and no pathologic reflexes were present. The liver was enlarged and was felt 5 cm. below the costal margin. There followed a slow and only partial physical recovery. Within 10 days the blood pressure returned to normal and the excretion of urine increased to 1200 cm. daily. (There is no statement concerning the blood pressure and flow of urine during the first days of the disease.) Ten weeks after delivery the heart rate ranged between 110 and 140; the blood pressure was 124/94; the rate of respiration was 12 per minute. The urine still contained albumin and a large number of white blood cells. The liver was 2.5 cm. below the costal margin.

The patient continued in a state of mental deterioration. She gradually became able to swallow solid food when it was placed in her mouth, and reacted to painful stimuli but made few spontaneous movements. The eyes followed a moving object, the mouth was spontaneously opened and closed, teeth clicked and a few unintelligible sounds were muttered. Most of the time she lay quietly in bed, paying no attention to her surroundings and not responding to stimuli or questions. Later, she was able to sit in a chair. She continued to lead a vegetative existence until her death 6 years later, on July 3, 1937.

* Received for publication, October 5, 1942.

Gross Examination

Postmortem examination revealed: (1) chronic suppurative pyelonephritis on the right (with streptococci in smears); (2) amyloidosis of kidneys, liver, spleen and myocardium; (3) an old tuberculous lesion in the apex of the left lung.

The brain weighed 579 gm. There was a severe bilateral atrophy of the frontal, temporal and parietal lobes (Fig. 1). The precentral and postcentral gyri and the occipital lobes were only moderately atrophic (Fig. 1). In the left frontal lobe all gyri of the convexity were atrophic, the atrophy being less pronounced at the base and on the median surface. In the right frontal lobe the atrophy was equally severe over the convexity, median surface and the base. In the left temporal lobe all gyri of the convexity and those of the base with the exception of the gyrus hippocampi were atrophic (Fig. 1); the atrophy extended into the parietal region, severely involving the angular and supramarginal gyri and large parts of the superior parietal gyrus (Fig. 1), and continued into adjacent parts of the occipital lobe. In the right temporal lobe all gyri with the exception of the midportion of the superior temporal gyrus and the gyrus hippocampi were destroyed, the atrophy continuing into the left angular and supramarginal gyri. Coronal sections showed a most severe cystic degeneration of the white matter throughout the brain, which in many areas exceeded that of the gray matter, the latter being frequently preserved (Fig. 2). Only at the base of both temporal lobes and in the right frontal lobe was the destruction equally severe in both the gray and white matter, reducing the convolutions to thin-walled cysts.

The caudate body, putamen and pallidum were moderately atrophic and the entire thalamus was greatly atrophic. The hypothalamus and the dorsal part of the pons were of normal size and appearance. The basilar part of the pons and numerous folia of the cerebellum were distinctly reduced in size.

Weigert preparations revealed advanced demyelinization in all atrophic areas, especially so in both parietal lobes and at the base of both temporal lobes, while in both superior temporal convolutions, operculum and hippocampal gyri a considerable amount of myelin was still preserved (Fig. 3). There was also considerable reduction of myelin in the corpus callosum, fornix and the mammillary bodies and only mild demyelinization in both occipital lobes and in the cerebellum.

Microscopic Examination

Histologic examination of the cortex showed preservation of a considerable part of the parenchyma. Even in the most severely destroyed

areas remnants of the cyto-architecture were visible. Usually the two or three upper layers could still be distinguished, while the lower layers were replaced by a spongy tissue (Fig. 4). In areas less severely affected usually the upper four layers survived, while in the motor cortex, operculum, occipital lobes, and in the islands the entire cyto-architecture could be recognized. In these latter areas there were numerous small perivascular foci of parenchymatous degeneration of the type described by Spielmeyer.[3] The neurons throughout the cortex showed various types of degeneration. In the most severely affected areas they were greatly shrunken; in others the so-called ischemic degeneration, frequently associated with incrustations, prevailed. There were changes in the neurons of the corpus caudatum, putamen, and in a milder form in the pallidum, similar to those of the cortex. However, there was no appreciable reduction in the number of nerve cells with the exception of the caudate nucleus. In the thalamus there was an extensive secondary degeneration of the parenchyma which was replaced by glial scars, especially in the anterior and lateral nuclei.

As already mentioned, the degeneration of the white matter was more severe than that of the gray, the severe destruction being present in the marginal strata and less frequently in the deeper parts (Fig. 4). In numerous areas there was a spongy state (Fig. 4), built of a delicate network of glial fibers occasionally interspersed with astrocytes (many of them of the giant variety), capillaries, a few gitter cells, scattered axis cylinders and remnants of myelin sheaths. The hypothalamus and the nuclei of the brain stem were normal, with the exception of the pontile nuclei and inferior olives, which were moderately degenerated. In the cerebellum there were extensive focal areas of degeneration in the cortex of both hemispheres, in the vermis, and in the dentate nuclei, and a diffuse moderately advanced demyelinization in both semilunar lobes.

The resorption of the destroyed tissue had been completed everywhere and there were no signs of tissue activity except for small scattered foci of proliferating microglia and a few gitter cells. Lipoids and pigments were not seen. The meninges were greatly thickened and fibrotic over all degenerated areas (Fig. 4). The blood vessels of the entire central nervous system showed no definite alterations with the exception of terminal thrombi in the large veins, but there were no remnants of old organized or recanalized thrombi or of old hemorrhages.

Numerous commissural, projection and association systems showed secondary degeneration. Incompletely demyelinated systems stood out in Weigert sections, while completely degenerated pathways could be

visualized in Nissl preparations because of gliosis. There was advanced gliosis in the cingulum, in the uncinate and in the superior longitudinal fasciculi. The corpus callosum and the anterior commissure were considerably demyelinated. Of the projection systems, the frontal, temporal and parietal thalamic radiations were degenerated as were also the frontopontile and temporopontile tracts. The pontocerebellar fibers were distinctly reduced in number. There was only a moderate reduction of myelin in the corticospinal tracts. The auditory and optic radiations were normal.

Comment

This case belongs to a variety of puerperal eclampsia which is characterized by a particularly severe destruction of one organ such as liver (Konstantinowitsch,[4] Ceelen [5]), kidneys (Klotz,[6] Bradford and Lawrence,[7] Griffith and Herringham,[8] Lloyd,[9] Jardine and Teacher,[10] Schüppel [11]), heart (Ottow [12]), or brain, as in this case. If we assume that the normal brain weight in our patient (who was 167 cm. tall) was approximately 1300 gm., we must conclude that at the time of death 60 per cent of the brain substance was resorbed.

The pathologic findings in the brain can be divided into primary and secondary. To the first group belong all changes directly caused by abnormalities of the metabolism of unknown nature during the acute phase of the disease; to the second such changes as appeared later secondary to extensive degeneration of the white and gray matter. To the former belong acute destruction of marginal layers of the white matter of the hemispheres, of the lower layers of the cortex, and of the gray matter of the cerebellum, and to the latter the degenerative changes of the commissural, association and projection systems.

For the understanding of the patho-anatomic changes it is important to bear in mind that the most advanced primary degeneration occurred in the marginal zones of the gray and white matter in which the destruction was so complete that remnants of the glial tissue which survived were able to build only a poorly organized spongy scar. This almost universal development of the marginal degeneration virtually severed the cortex of the hemispheres from the white matter, producing a picture closely resembling that described by Nissl [13] following experimental decerebration in rabbits. This dissociation of the cortex from the white matter occurred in extensive areas of the frontal, temporal and parietal lobes, *i.e.*, those parts of the brain which are mainly concerned with higher mental activity, accounting for the sudden and profound mental deterioration.

Interpretation of the pathophysiologic mechanism responsible for

the atrophy is difficult since at the time of death the destroyed tissue was resorbed, no longer permitting a comparison with histologic changes in acute stages of this disease. According to our present state of knowledge, the latter is characterized by (1) diffuse toxic degeneration of the parenchymatous cells with disintegration of the cytoarchitecture, (2) small areas of necrosis in the gray and white matter, (3) hemorrhages, (4) thrombosis, frequently with "hyaline" degeneration of the vessel wall, and (5) edema of the brain.

None of these findings can satisfactorily explain the unusual extent of damage in the present case. There is no evidence that the destruction was due to thrombosis since no remnants of old thrombi were found and the vessels appeared to be normal, nor could hemorrhages taking place during the acute stage be made responsible for the atrophy since no accumulation of blood pigment or other remnants of organized hemorrhages were present.

It seems reasonable to assume that the lesions were the result of a primary necrosis of the tissue, similar to the case of cardiac degeneration of Ottow,[12] and the question arises as to the manner in which it took place. Two possible pathogenetic factors, or a combination of them, must be considered: (1) functional disturbances of circulation, (2) toxic influences.

Functional disturbances of the circulation, such as angiospasm, have been considered an important factor in eclampsia. Bodechtel [14] described degeneration of the calcarine area, which he attributed to such disturbances since the vessels in the destroyed area showed no organic changes. This view was challenged by Heynemann,[15] who pointed out that similar vasospasms are also present in other disorders which have neither etiologically nor pathologically anything in common with eclampsia, such as atherosclerosis of the kidneys, glomerulonephritis, and many others. He concluded that the "vascular factor" is merely a symptom of eclampsia and is pathogenetically of no significance. While Heynemann's conclusions may apply to renal conditions, it is doubtful whether they can apply to the pathology of the brain. Spielmeyer [3] showed conclusively that functional changes in circulation may very well cause focal degenerative lesions in the cortex under a variety of conditions, such as physical trauma and hypertension, and also in eclampsia and other intoxications. The morphology of the lesions is always similar and permits no differential diagnosis. While the lesions described by Spielmeyer were limited in size, Malamud and Boyd [16] demonstrated that functional disorders in vessels which are morphologically apparently normal may cause a breakdown of the entire vasomotor system of the cortex resulting in extensive

ischemic necrosis. It must therefore be considered as likely that functional disorders of the circulation may produce extensive cortical damage, but this is not known to have occurred in the white matter, which is so extensively damaged in our case. Functional disturbances of vascular nature unquestionably did occur in the acute stage, since small perivascular foci of degeneration were present in many areas of the cortex, but these foci remained small and can in no way account for the extensive degeneration either of the gray or the white matter nor contribute to the understanding of the pathogenesis. Since the white matter is much less rich in vessels and is therefore much less dependent on oxygen supply, it is difficult to attribute the necrosis of the subcortical tissue to the "vascular factor." Some considerations seem to suggest a different pathophysiologic mechanism: the destruction of the white matter is most severe in the marginal (subcortical) layers, *i.e.*, in those parts in which toxic influences are frequently at work. In this connection we call attention to conditions in which disturbances of metabolism cannot be denied, such as Wilson's disease and many other disorders of the liver in which the degeneration of the marginal layers of both gray and white matter attain extensive proportions. Similarly, in fatal nitrous oxide poisoning the same areas of the brain are destroyed. Therefore, it seems logical to assume that toxic influences are mainly responsible for the destruction of brain tissue in this case.

While the permanent damage was confined to the brain, the pathologic changes of the internal organs are of some importance, as contributing factors. The enlargement of the liver in the early days of the disease suggests acute involvement of this organ, which was later relieved, while the pyelonephritis apparently assumed a chronic course finally resulting in amyloidosis in various organs.

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[*Illustrations follow*]

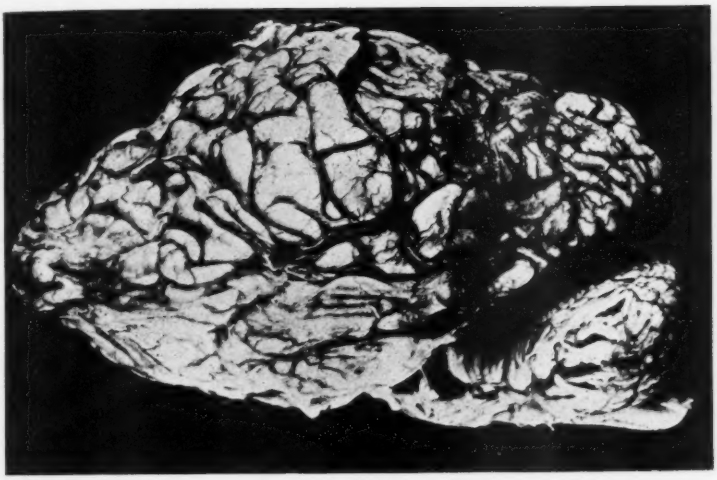
DESCRIPTION OF PLATES

PLATE 82

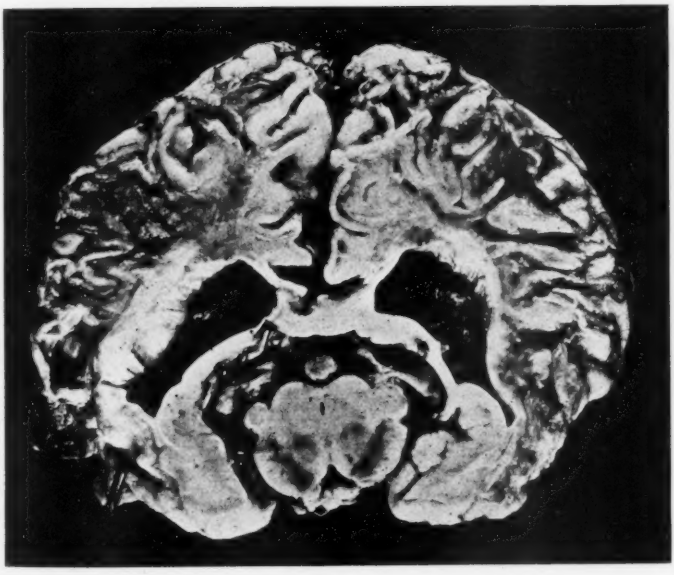
FIG. 1. Severe atrophy of the frontal, temporal and parietal regions.

FIG. 2. Advanced cystic atrophy of the white matter in both hemispheres; cortex severely involved in both temporal lobes.

1



2



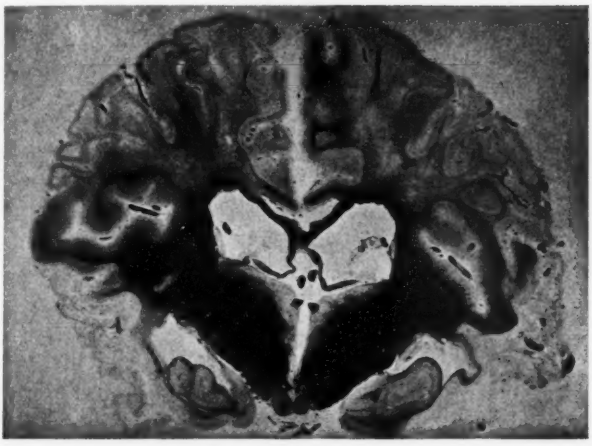
Lowenberg and Lossman Atrophy of the Brain Following Eclampsia

PLATE 83

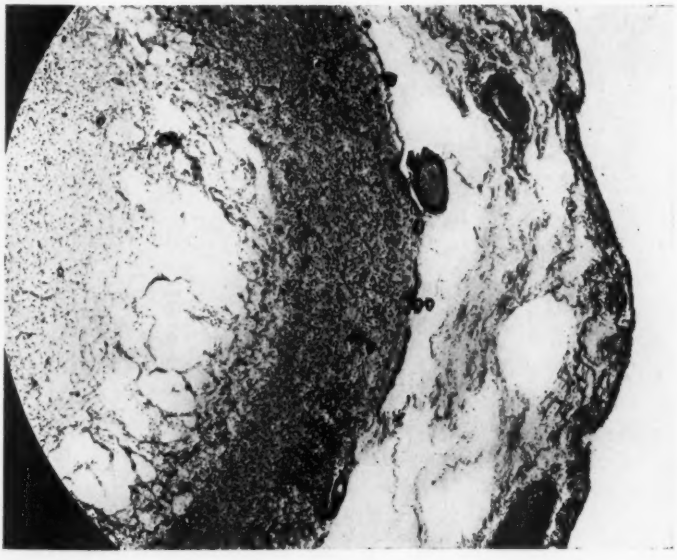
FIG. 3. Weigert preparation, demonstrating demyelinization in both parietal and large parts of the temporal region.

FIG. 4. Nissl preparation, demonstrating spongy state in the marginal stratum; meninges considerably thickened. × 20.

3



4



Lowenberg and Lossman Atrophy of the Brain Following Eclampsia

MEDULLARY INVOLVEMENT IN TETANUS *

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In recent literature, reports of histopathological studies of the alterations that occur within the nervous system in tetanus are lacking. This is unusual when one considers the frequency of this disease and the large number of studies on its pathogenesis and treatment. No doubt one of the chief reasons for this paucity of pathological studies is the general impression that tetanus produces very little anatomical damage to the nervous system. Many investigators have reported such negative observations in spite of accurate studies (Wagner,[1] Leyden,[2] Tauber,[3] Vincenzi,[4] Nageotte and Ettlinger,[5] Courmont, Doyen and Paviot [6] and Sjövall [7]). However, it is difficult to believe that a disease which produces such dramatic neurological symptoms can avoid leaving structural damage in at least a few of the more severe cases. It seems much more likely that this disease is often so fulminating in its course that insufficient time elapses for the actual tissue changes to become microscopically discernible. It was for this reason that detailed pathological studies were undertaken in 12 fatal cases of tetanus, in an attempt to locate and, if possible, correlate any discovered changes of the nervous system with the durations of the illness.[8] It was apparent from these studies that in all cases of tetanus in which the illness lasts over 3 days, definite changes do occur within the nervous system. Up to the fifth day of the illness these changes are limited to the nerve cells and consist of mild swelling and chromatolysis. If the patient survives beyond the fifth day, there may occur much more extensive lesions consisting of perivascular glial nodules, and perivascular demyelinization. At the time of these original studies, my interest was attracted by the tendency of the lesions, in some cases, to be most intense within certain cranial nerve nuclei. Such a selective localization frequently correlated fairly closely with many of the clinical symptoms presented by the patients. In order to study more carefully this distribution of the cellular lesions, serial sections were made of all the cranial nerve nuclei, of the spinal cord at various levels and of various cortical areas in a case of tetanus, showing what appeared to be definite signs of medullary involvement throughout the course of the illness. The findings in this case comprise the present report.

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Report of Case

W. P. (hospital no. 722000), a farmer, 41 years old, had a wart removed from his left middle finger 2 weeks before admission to the hospital. He continued to work on his farm and felt well until 10 days later when he first noticed some stiffness in his jaw. By the next day he was unable to open his mouth and had some difficulty in swallowing. He became restless and irritable and was taken to the local hospital where he received some tetanus antitoxin. In spite of this therapy, he continued to show a progression of symptoms, developing periodic attacks of generalized tonic spasms of most of his musculature. On the third day of his illness he was transferred to the University Hospital. On admission the patient was conscious and co-operative, but the slightest stimulus precipitated a generalized tonic spasm of most of his musculature. He had a marked trismus. Even at this early period it was noticed that the patient had definite cardiac and respiratory irregularity in spite of the absence of any discernible pathology in these organs. His breathing was particularly involved, at times being extremely slow or very rapid, shallow and labored and sometimes being normal. The pulse also varied from a firm, full regular beat to rapid regular or irregular pulsations which occasionally were difficult to palpate. The patient was treated with tetanus antitoxin intravenously, receiving 80,000 units during the first 48 hours of hospitalization. His muscular spasms were so well controlled by avertin that throughout most of his stay he remained well relaxed. In spite of this medicinal control of the muscular involvement, the cardiac and respiratory irregularities nevertheless continued to become more severe. His respirations became more labored and irregular and the patient expired, apparently from medullary paralysis, after a hospital stay of 3 days and on the sixth day of his illness.

Pathological Studies

There were no gross changes within the nervous system.

Histological Studies

Sections from various parts of the nervous system were prepared by Nissl's, Weil's and the hematoxylin-phloxin B technics.

Cerebral Cortex. The gray matter of the hemispheres revealed surprisingly few changes. Most of the nerve cells were intact (Figs. 1 and 2). An occasional cell showed mild perinuclear chromatolysis. In a few cells, the perinuclear Nissl granules, although present, were very fine while the peripheral granules were large and heavily pigmented. In none of the neurons were changes noted either in the nuclei or in cell processes.

There were no alterations within the glial elements. Many of the small vessels showed a moderate degree of endothelial swelling and some proliferation, but in none was the lumen markedly attenuated or closed.

Cerebellum. Many of the Purkinje cells revealed a mild reduction in the intensity of their staining properties but were otherwise structurally intact. There were no changes within the granular elements or within the white matter.

Midbrain. The large cells of the lateral oculomotor nuclei were intact. Their Nissl granules were large and irregular and stained very deeply (Fig. 3). Dorsal to these cells were the small pyriform cells of the nucleus of Edinger and Westphal. Normally these cells contain but a thin rim of cytoplasm filled with heavily stained granules, and because of this appearance one might suspect some structural alteration even within normal elements. However, careful study revealed no pathological changes within these cells. Their nuclei were large, well formed and unaltered.

An occasional cell within the nucleus ruber showed a mild fading out of Nissl granules and the presence of an occasional cytoplasmic vacuole. None had any nuclear alterations. The substantia nigra appeared intact.

The vessels within the midbrain were uninvolved. There was no endothelial reaction. No alterations of myelin or of the glial cells were detectable.

Trochlear Nucleus. The large nerve cells of this nucleus were anatomically intact.

Midpons. The motor (masticator nucleus) of the trigeminal nerve, especially on the right side, revealed most extensive and significant alterations (Fig. 4). Most of its cells were shrunken and pyknotic. In many, only small fragments of cytoplasmic material remained, irregularly attached to an apparently normal or shrunken nucleus. In those cells with intact cell bodies, chromatolysis was complete with the cytoplasmic material often being replaced by large vacuoles. The tinctorial properties of some of the cells were partially or completely lost, leaving only a faint outline of the original neuron or resulting in a ghost cell formation. Scattered throughout these severely altered elements were a few with apparently normal architectural arrangement, but even these did not have the appearance of the normal cells, being smaller and containing much less cytoplasmic material. The small vessels within this nucleus showed a moderate degree of endothelial proliferation and a marked vascular congestion. No glial changes were apparent.

The corresponding nucleus on the left side was much less severely involved, although definitely damaged. Here most of the cells showed only swelling and partial chromatolysis. Only scattered elements presented diffuse involvement. In some cells the Nissl substance stained very lightly, while in others it was entirely absent or replaced by intracellular vacuoles. The cell nuclei were usually intact although occasionally swollen and eccentrically placed.

The pontine (sensory) nuclei of the fifth cranial nerve just lateral

to the motor nuclei normally present cells which are somewhat smaller than the motor elements. However, in these sections they appeared larger due to the extensive destruction and shrinkage of the motor cells (Fig. 5). The sensory elements revealed a fairly large, centrally placed nucleus surrounded by a somewhat irregular cell body. Some of the cells were slightly elongated. Their Nissl granules were very fine and stained very lightly although their architectural details were easily made out with higher magnifications. No nuclear changes were visible. These elements were surprisingly healthy, especially when contrasted with the cells of the adjacent motor nucleus. There was a mild congestion but no endothelial proliferation in this nucleus.

The scattered cells of the superior vestibular nuclei were normal. Their cell bodies were distinct and well outlined. The Nissl granules were fairly large and evenly distributed throughout the cell body.

The cells of the pontine nuclei were also well preserved and showed no consistent alterations. Only an occasional cell revealed a slight fading out of some of its tigroid bodies.

Lower Pons. The abducens nuclei were uninvolved. All of the cells were filled with large, deeply stained Nissl granules. The cell nuclei were centrally placed and appeared to be healthy.

The facial nuclei showed very little change (Fig. 6). An occasional cell revealed a mild focal tigrolysis. There was a slight variation in the size of some of the cellular elements but no structural abnormality.

In the vicinity of both the abducens and facial nuclei there was marked congestion but no hemorrhages. No endothelial changes were observed.

The dorsal and ventral cochlear nuclei as well as the lateral vestibular nuclei were for the most part uninvolved. Scattered cells showed very mild changes, involving primarily the tigroid substance. In some the Nissl granules were partially absent, while in others these granules, although not reduced in number, showed a tendency to stain more intensely around the cell periphery, producing the appearance of a perinuclear chromatolysis. In the ventral cochlear nuclei, a few cells showed a slight irregularity and a mild retraction of their processes. No nuclear changes were apparent. Many of the vessels in the vicinity of these nuclei exhibited a mild endothelial swelling. An occasional vessel was completely occluded by endothelial proliferation. Congestion was very intense but no hemorrhage had resulted.

The cells of the spinal tract of the fifth cranial nerve were not distinctly made out. In most sections they were few and very small. Their tigroid granules, although very fine, appeared intact. Their nuclei were often eccentrically placed.

The components of the superior olive were very irregular in shape and size. The larger cells contained deeply stained, evenly distributed Nissl granules about a centrally placed nucleus. An occasional cell showed an early perinuclear tigrolysis. In the smaller cells the Nissl granules were very fine, stained very lightly, and were more difficult to make out; their nuclei were often eccentrically placed.

Upper Medulla. The cells of the solitary fasciculus were small, and irregular in outline. Most of their tigroid substance was very fine and evenly distributed throughout the cytoplasm; a few cells contained heavier, more intensely staining granules interspersed among the finer ones. These heavy granules were evenly distributed and showed no peripheral arrangement. The preservation of structural detail indicated that this cytoplasmic appearance might be normal for these cells. Unquestionable injury, however, occurred to many elements within this nucleus. Such showed an eccentrically placed nucleus which often stained very lightly, having lost some of its tinctorial properties. A few cells contained little or almost no cytoplasmic material, leaving an isolated pyknotic or lightly stained nucleus. Even an occasional swollen ghost cell could be observed. From cursory study it appeared that about one-half of the cells within this nucleus had undergone some type of structural alteration.

Middle Medulla. The dorsal nucleus of the vagus was more severely injured than any other nuclear group in the nervous system. Hardly a normal cell was to be found. The most constant alteration was a perinuclear chromatolysis, with only a thin rim of Nissl granules remaining around the periphery of the cells (Figs. 7 and 8). Many of the cells were swollen, rounded and had lost much of their tinctorial properties. Many of their processes were shrunken, fragmented, or had entirely disappeared. Most of the neurons were small and appeared to have lost considerable cytoplasmic material. The cell nuclei were also altered, many being eccentrically placed, swollen and even pyknotic.

(Sections through this nucleus were also available from a second case of tetanus, the patient dying from an apparent medullary involvement. In this case the dorsal nucleus of the vagus revealed even more advanced and more permanent alterations. Most of its elements were extremely shrunken and pyknotic (Fig. 9). The neurons appeared as small dark masses within which no structural details could be made out. Most of their processes were shortened and narrowed, or were fragmented or entirely absent. In both cases hardly a normal cell was found throughout the nuclei. Congestion was prominent in the vicinity of the nuclei but no endothelial changes were found.)

Nucleus Ambiguus. The cells in this nucleus were not nearly as

severely damaged as were those of the dorsal nucleus. An occasional cell was swollen, its processes being fragmented or entirely absent, giving the cell a rounded appearance. The Nissl granules in these cells were reduced in number and generally were very finely granular, with only a few heavy granules scattered near the periphery of the cell body (Fig. 10). None of the cell nuclei appeared involved.

The large cells of the hypoglossal nuclei, although lying almost adjacent to the greatly damaged dorsal nucleus of the vagus, showed no histological alterations (Fig. 11). All of the architectural details of their elements could be very easily discerned. There was, however, a marked congestion but no endothelial change.

Spinal Cord. The cellular elements within the cord were surprisingly well preserved. Most of the anterior horn cells showed no changes (Fig. 12). Interspersed among these predominantly healthy elements were a few showing a mild fading out of the Nissl granules or even a beginning perinuclear chromatolysis. None of the anterior horn cells showed nuclear changes. The scattered cellular changes were not limited to any particular segment of the cord, but were irregularly and diffusely scattered throughout. There was a mild congestion within the cord but no endothelial change.

Discussion

It is apparent from this study that in certain cases of tetanus the toxin, though distributed throughout the nervous system, appears to have a specific action upon certain cell groups, a selectivity that may correlate the elements of the clinical picture presented by this illness. In the present case there can be no doubt that tetanus toxin showed a selective action upon two cell groups; namely, the motor nucleus of the trigeminal and the dorsal nucleus of the vagus, the involvement of the latter doubtless producing the respiratory failure. From the clinical symptoms in tetanus, it is apparent that the toxin produces functional impairment in almost every case, but in those cases in which the course of the illness is very rapid and of but a few days' duration, insufficient time elapses to allow structural changes to become apparent. When the duration of the disease is sufficiently prolonged, usually beyond the fifth day, visible changes occur within the nervous system. The first elements to become involved are the nerve cells. The distribution of this cellular damage is most irregular and appears to be widely scattered throughout the nervous system. Most of the cellular alterations are mild and consist primarily of swelling and perinuclear chromatolysis. Such changes are reversible and may disappear after recovery from the illness or after neutralization of

the toxin by antitoxin. Within scattered cells or groups of cells there do occur more severe and definitely irreversible changes, some consisting of fragmentation of the cell processes, vacuolization and fragmentation of the cell body, pyknosis of the nuclei, and even pyknosis of the entire cell, or ghost cell formation.

Most of the investigators studying the possible pathological changes in tetanus have limited their studies to the cells within the spinal cord, and their reports have varied from absolutely no alterations (Leyden,[2] Tauber,[3] Vincenzi,[4] Nageotte and Ettlinger[5]) to most extensive changes (Tauber,[3] Sjövall,[7] Goebel,[9] Matthes,[10] Elischer,[11] von Halban,[12] Barros[13]). Most investigators seem to agree that the chief damage occurs to the motor cells of the cord, and almost every degree of cell damage has been reported. Generally, however, the cell alterations have been mild and widely scattered throughout all segments of the cord with no tendency to localize. Sjövall, from his studies, suggested that the cell changes in tetanus were to be correlated with the tetanic motor irritation and, therefore, occurred on the side and in the region of the cord that supplied the involved limbs. These observations have not been substantiated in the literature or from my studies. In contrast to much of the literature, changes within the cord elements in my cases were strikingly scanty and even those present were mild and of a definitely reversible nature.

Cellular alterations in tetanus, although most frequently studied within the spinal cord, also appear within the rest of the central nervous system. Sjövall,[7] Elischer,[11] von Halban,[12] Minassian,[14] Joukowsky[15] and Ewing[16] have all recorded alterations within the cranial nerve nuclei or within the motor cortex of man and experimental animals. Elischer observed some paling and pyknosis within the cells of the 5th and 7th cranial nerves although the cell architecture was intact. Von Halban described vacuolization and extensive peripheral chromatolysis within the cells of the motor cortex and the 7th and 12th cranial nerve nuclei. Joukowsky described a vascular dilation within the medulla but did not mention any cellular changes. None of these investigators made an attempt to establish the presence of a definite selectivity of the tetanus toxin to certain cranial nerve nuclei. From my histological studies it seems evident that in certain cases of tetanus the toxin does have a specific affinity for certain cranial nerve nuclei, producing extensive and permanent cellular damage. The specific selectivity of the motor nucleus of the 5th cranial nerve and the dorsal nucleus of the vagus is most interesting when one considers the close correlation of these pathological alterations to the clinical symptoms presented by the patient.

Death in tetanus has generally been assumed to result from three causes; namely, exhaustion, circulatory failure from the great demand made upon the heart, and, finally, asphyxia due to spasm of the glottis, diaphragm and intercostal muscles. Death from medullary involvement has not been given very serious consideration. It is difficult to observe such specific focal damage to important medullary nuclei, as has been demonstrated in the foregoing case, without concluding that certain cases of this disease must terminate fatally due to severe damage to these centers with resultant cardiac or respiratory failure. Such a conclusion can be verified clinically when one observes cases in which, in spite of the absence of severe convulsions or in spite of adequate medicinal control, the patient continues to show marked cardiac and respiratory irregularities and finally dies of an apparent respiratory failure. The possibility of such cerebral involvement in tetanus must force one to be more guarded in his prognosis of this illness even in the face of apparent improvement and medical control.

Conclusions

1. Detailed pathological studies were undertaken in a case of tetanus showing definite signs of medullary involvement throughout the course of the illness.

2. Definite changes were observed within certain selected areas. The most extensive involvement occurred within the motor nuclei of the 5th and the dorsal nuclei of the 10th cranial nerves. These nuclei showed alterations within almost every nerve cell, the changes often being of a permanent and irreversible nature. The rest of the nervous system presented but scattered and usually minor changes.

3. The selectivity of the tetanus toxin for specific cranial nerve nuclei suggests the possibility that some deaths in this disease may be due to medullary involvement, with resulting respiratory or cardiac failure.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

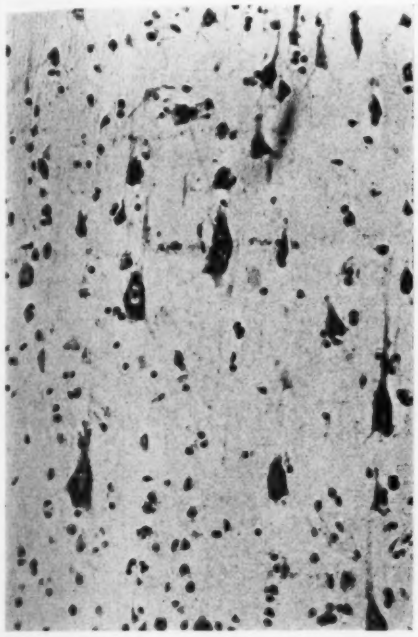
PLATE 84

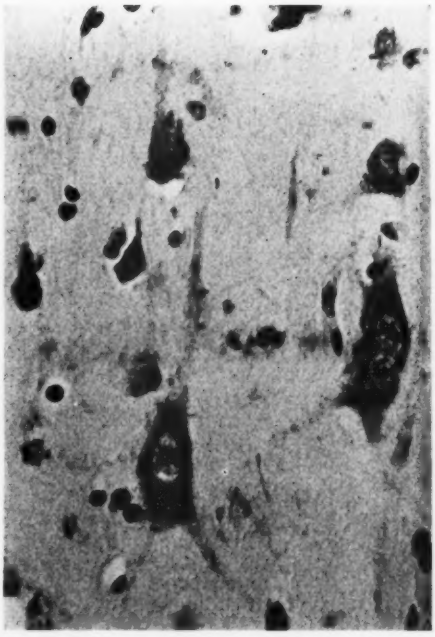
FIG. 1. Motor cortex. The cells appear normal. There is no apparent increase in the interstitial elements. Nissl stain. × 150.

FIG. 2. Motor cortex. High-power photomicrograph through the area in Figure 1, demonstrating in more detail the normal cyto-architecture of the nerve cells. Nissl stain. × 350.

FIG. 3. Oculomotor nucleus. The nerve cells as well as the interstitial elements show no alterations. Nissl stain. × 275.

FIG. 4. Motor nucleus of the 5th cranial nerve. The cells show extensive damage consisting of almost complete chromatolysis, disappearance of the cell processes, shrinkage of the cell body, fragmentation and pyknosis. Even the nuclei have been damaged in some of the neurons. Nissl stain. × 275.





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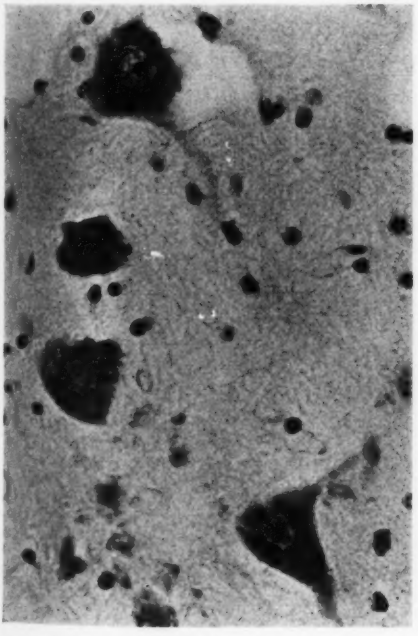

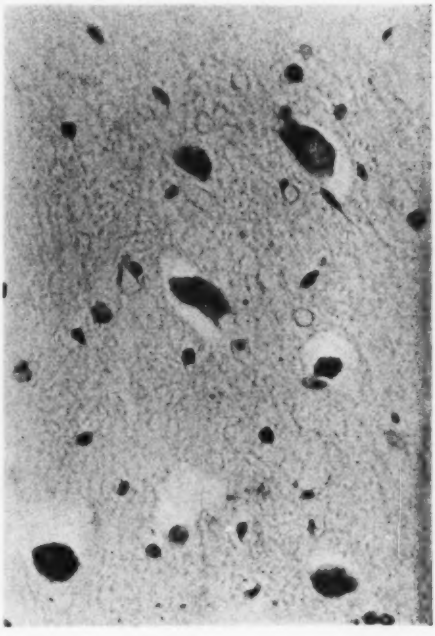

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Medullary Involvement in Tetanus

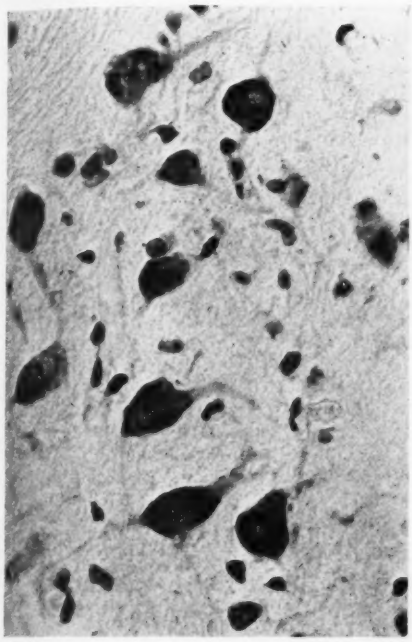
Plate 85

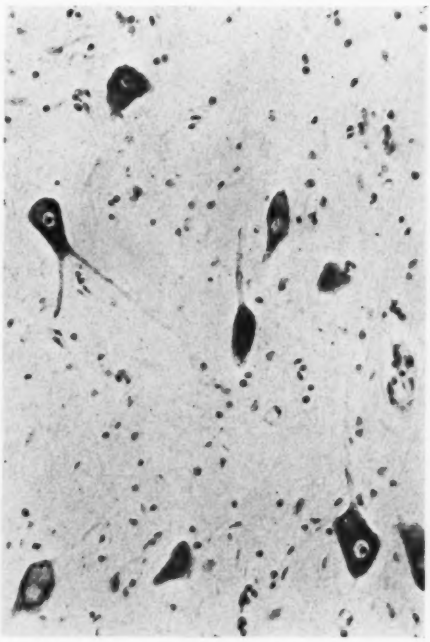
Fig. 5. Sensory nucleus of the 5th cranial nerve. These cells, in contrast to the motor elements, are uninvolved. Their architectural details can easily be made out. Nissl stain. × 275.

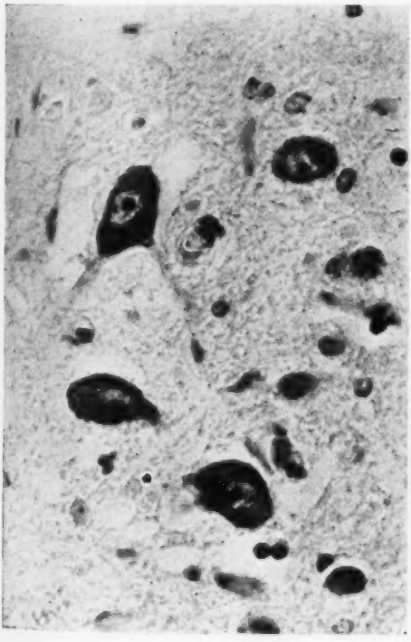
Fig. 6. Facial nucleus. The nerve cells are intact. A single neuron in the lower portion of the field contains a large cytoplasmic vacuole and shows a mild chromatolysis. Nissl stain. × 150.

Fig. 7. Dorsal nucleus of the vagus nerve. This control section was taken from an apparently normal nucleus. These cellular elements may be compared with those in Figures 8 and 9 which were taken from cases of tetanus. Nissl stain. × 275.

Fig. 8. Dorsal nucleus of the vagus nerve. There is characteristic perinuclear chromatolysis in almost all the cells. The cell processes have been partially destroyed, but the nuclei appear uninvolved. Nissl stain. × 275.







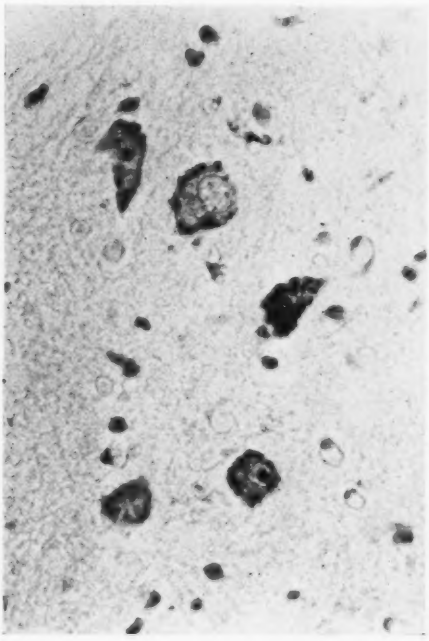


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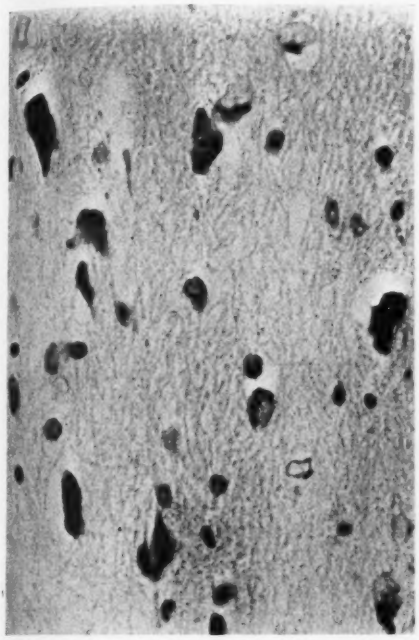
PLATE 86

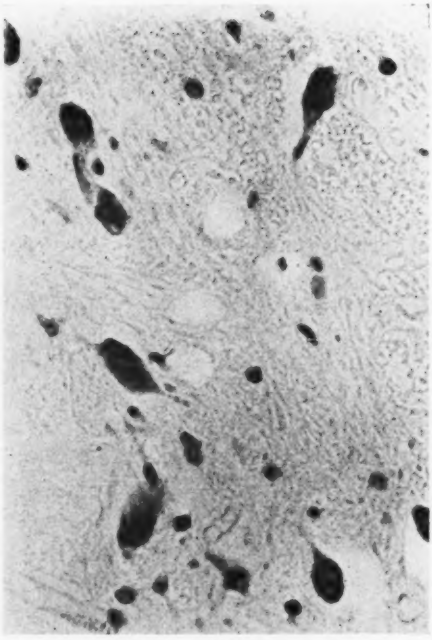
FIG. 9. Dorsal nucleus of the vagus nerve. This photomicrograph demonstrates a more advanced stage of the cellular damage. The neurons are shrunken and pyknotic. These changes are no doubt of an irreversible nature. Nissl stain. × 275.

FIG. 10. Nucleus ambiguus of the vagus nerve. There is early tigrolysis and beginning cytoplasmic shrinkage. Some of the cell processes have disappeared. Nissl stain. × 275.

FIG. 11. Hypoglossal nucleus. These cells are uninvolved even though they are situated very close to the severely damaged dorsal nucleus of the vagus. Nissl stain. × 275.

FIG. 12. Spinal cord. This photomicrograph demonstrates the anterior horn cells. Most of the cells are intact, although an occasional one does show a mild diffuse or even perinuclear chromatolysis. Nissl stain. × 275.





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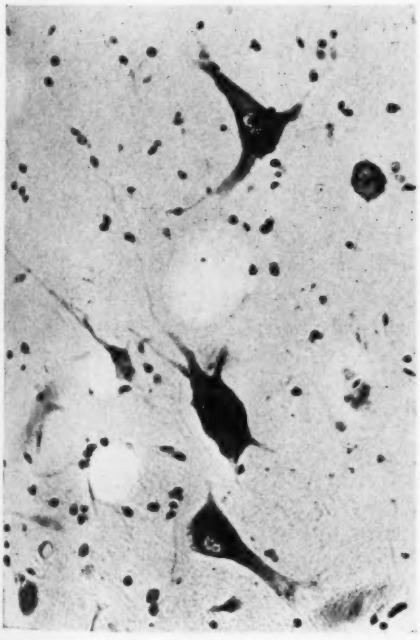

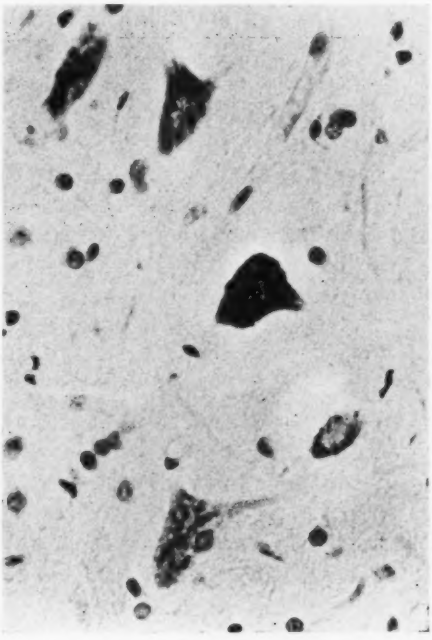

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Medullary Involvement in Tetanus

TUBERCULOSIS OF THE TONSILS *

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Disagreement exists as to the mode by which the tubercle bacillus infects the faucial tonsils. Weller [1] studied 204 cases of active tonsillar tuberculosis and came to the conclusion that in 90 per cent of the cases the infection had arisen in the crypts. Usually the infection was unilateral and there was no obvious tuberculosis elsewhere in his patients. He described 16 cases in which the tubercles were located in the follicles, often in the germinal centers. Most of these were bilateral infections. Weller decided that the cryptal type of infection was primary (in the sense of exogenous) and the follicular type a secondary, blood-borne infection. The views of this investigator, based as they are on the histology of a large number of lesions, seem well grounded. That they are not universally accepted is shown by the statement of Hansel [2] that "both direct and indirect evidence make it probable that the tonsils are usually infected by the blood stream." Libin and Travushkina [3] stated that the difficulty of making a clinical diagnosis of tonsillar tuberculosis exists because the pathological process begins in the depths of the tonsil and that this origin is in favor of a blood stream infection. This last seems to be an unwarranted deduction since the crypts extend deeply into the tonsil and an infection originating at the base of a crypt would originate in the depths of the tonsil.

Schlittler [4] had previously examined 48 tonsils in a series of 89 cases of tuberculous lymphadenitis. He decided that these were examples of primary tuberculosis of the tonsil because (1) 73 per cent were unilateral, (2) 63 per cent of the patients were under the age of 12, (3) sputogenic infection seemed contraindicated by the clinical histories. Later, he reconsidered the facts after examining the tonsils in another series of 41 cases of tuberculous lymphadenitis. In this group most of the patients were over 12 years and the percentage of unilateral infection was lower. His final conclusion was that the majority of the cases were not primary but either post-primary or secondary hematogenic. The differences of opinion which exist have been commented on by Long, Seibert and Gonzalez [5] and the literature in this connection reviewed. They stated that Schlittler believes most infections to be hematogenous, but this overlooks Schlittler's post-primary group. The pathogenesis of tonsillar tuberculosis in cases of pulmonary disease chiefly interested Long and his associates. They

* Received for publication, September 4, 1942.

studied a considerable number of cases and found that in open tuberculosis of the lungs the tonsillar infection was frequently bilateral and apparently originated in the crypts. There was nothing to support the hematogenic mode of infection. This is in agreement with the ideas of Weller.[1] The clinicopathological data on the cases studied in this present paper support Weller's views.

Material and Methods

In the 19,000 tonsillectomies done at the Henry Ford Hospital from 1922 to 1941 inclusive, there have been 35 cases of active tonsillar tuberculosis. At this clinic all tonsils are examined microscopically. A single section is cut at right angles to the mucosa through the long axis of the tonsil. The diagnosis of tuberculosis was made in those cases which showed typical active tubercles. All available clinical and laboratory data were collected and the morphological picture of the diseased tonsils was reviewed in an attempt to establish the pathogenesis for this series.

In this study the initial assumptions were that a cryptal infection is due to the passage of the tubercle bacillus through the mucosa (or possibly through ulcerations at the bases of the crypts); that tubercles found in relation to the follicles and germinal centers in the absence of relation to the crypts signify a hematogenous spread to the tonsil; that lymphatic spread can be ignored because the tonsil has no afferent lymphatics and retrograde spread is unlikely. The results of the study were not such as to require alteration of the assumptions. The following classification was used:

1. Unilateral
   - A. Cryptal
     - (1) Primary (by inhalation or ingestion)
     - (2) Post-primary (by inhalation, ingestion, or sputum)
   - B. Follicular
2. Bilateral
   - A. Cryptal
     - (1) Primary
     - (2) Post-primary
   - B. Follicular

The number of cases in each category and the distribution of the cases by serial numbers are shown in Table I.

Unilateral Infections without Pulmonary Tuberculosis

Case 1. A child, 3 years old, was admitted with a history of frequent bouts of upper respiratory infection since the age of 2. No exposure to tuberculosis known. X-ray studies showed hilar tuberculosis and Pott's disease of the seventh dorsal vertebra. Tonsillectomy disclosed a unilateral cryptal infection.

Case 5. A girl, 13 years old, was admitted with an enlarged node on the right side of the neck of 3 years' duration. There had been a sudden increase in size 3 months previously. No history of tuberculosis. Tonsils were enlarged and scarred. The child had been examined previously at another hospital and all findings, including roentgenograms of the chest, were negative. There was a nontender, nonfluctuant node on the right side of the neck, about the size of a hickory nut. Tonsillectomy was done on November 9, 1931. There was a unilateral cryptal tuberculosis. The patient was seen again in 1941, at which time she seemed to be in good health.

TABLE I

Distribution of Cases According to Subdivisions of the Classification

Classification*	Number of cases	Case numbers†
1.	27	1, 5, 6, 7, 8, 11, 12, 13, 14, 15, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34, 35
1.A.	20	1, 5, 6, 7, 8, 11, 12, 13, 14, 15, 18, 20, 23, 24, 25, 26, 28, 29, 30, 31
1.A.(1)	15	1, 5, 6, 7, 8, 11, 12, 14, 18, 23, 24, 25, 29, 30, 31
1.A.(2)	5	13, 15, 20, 26, 28
1.B.	None	None
2.	8	2, 3, 4, 9, 10, 16, 22, 32
2.A.	6	3, 9, 10, 16, 22, 32
2.A.(1)	3	3, 9, 32
2.A.(2)	2	10, 16
2.B.	2	2, 4

* The notations under this heading refer to the classification given in the text.

† Of the 27 cases of unilateral tuberculosis only 20 can be completely classified. The remaining 7 are cases 17, 19, 21, 27, 33, 34 and 35. Whether cases 17, 19, 27, 33 and 35 were cryptal or follicular could not be determined. Both tonsils were removed in case 21, but only one reached the laboratory. Case 34 is probably 1.A.(1) but the clinical information is incomplete. One of the bilateral infections, case 22, could not be completely classified because of lack of evidence. Probably it falls under 2.A.(1).

Case 6. A child, 6 years old, was admitted for a routine tonsillectomy. There was no history of exposure to tuberculosis. Tonsillectomy was done on May 22, 1929. There was a mild unilateral cryptal infection. Roentgenograms of the chest on June 24, 1929, were negative; those of June 28, 1930, showed enlarged hilar nodes. On September 17, 1932, roentgenograms of the chest showed a widened hilar shadow but no calcified nodes; those of November 4, 1933, were similar, and on October 19, 1935, a tubercle of Ghon was seen in the right fourth interspace. Throughout this time the child remained in good health.

Case 7. A child, 9 years old, was brought in at the request of school authorities for a routine tonsillectomy and adenoidectomy. Physical examination was essentially negative and the lungs were stated to be negative. The tonsils were enlarged and the anterior cervical nodes palpable. Tonsillectomy was done on January 19, 1931. Microscopically there was a cryptal infection in one tonsil. The other was uninvolved. The child was not seen again at this clinic.

Case 8. A white girl, 18 years old, was first seen on February 20, 1926, complaining of large nodes at the angle of the jaw on the left side of 4 months' duration. Physical examination was essentially negative. Tonsillectomy on February 23, 1926, disclosed an extensive cryptal infection in one gland. Shortly afterward she developed a draining cold abscess on the left side of the neck. In 1938 she was in fairly good health and the infection was quiescent. There was never any evidence of pulmonary tuberculosis.

Case 11. A white boy, 27 months old, was brought in because of cervical adenitis of 3 weeks' duration. An uncle had osseous tuberculosis. A brother, 10 months of age, had died of "mucous colitis" a few weeks previously. The child showed an enlargement of the entire group of right cervical lymph nodes without redness, pain, or fluctuation. Tonsillectomy on April 4, 1927, disclosed a unilateral cryptal infection. Roentgenograms on May 3, 1927, were read as showing no hilar enlargement or parenchymal involvement. On March 9, 1928, one of the nodes on the right side of the neck was incised and a tuberculous abscess found. Roentgenograms on January 24, 1929, showed hilus enlargement but no definite tuberculosis.

Case 12. A white girl, 6 years old, was brought in for routine tonsillectomy. The history and examination were negative. Tonsillectomy on October 23, 1926, disclosed a mild unilateral cryptal infection. Roentgenograms on November 4, 1926, showed a calcified node in the neck on the right side, as well as some calcified hilar nodes.

Case 14. A white boy, 5 years old, was brought in because his father thought that he should have his tonsils removed. He had always been healthy. General physical examination was negative. Tonsillectomy was done on August 18, 1927. Microscopically there was a unilateral cryptal tuberculosis. The child was seen again for a recheck on September 14, 1927, and the lungs were stated to be negative.

Case 18. A child, 5 years old, was admitted whose mother had shown a positive sputum on several occasions. Roentgenograms on December 13, 1934, showed calcification in the right hilus and possibly in the parenchyma on the right. Tonsillectomy on January 3, 1935, disclosed a severe localized unilateral infection. This child was last seen in 1941, at which time there were areas of calcification in the hilus but no evidence of parenchymal disease.

Case 23. A white girl, 20 years old, came in with the complaints of bronchitis, chronic cough and lack of energy. Physical examination was essentially negative except for deflected septum and hypertrophic tonsils. Tonsillectomy was done on November 16, 1929. Microscopically there was a unilateral cryptal infection. Some of the tubercles had a little central necrosis but there was no caseation. The patient did not return for a recheck.

Case 24. A boy, 4 years old, was admitted whose father had pulmonary tuberculosis. On December 7, 1931, the child gave a positive reaction to 1/10 mg. O.T. A roentgenogram made on the same day showed hilar accentuation which was not definitely tuberculous. Tonsillectomy was done on May 6, 1932. There was a mild unilateral cryptal infection. On March 10, 1933, a cold abscess ruptured in the right groin.

Case 25. A white man, 27 years old, was admitted for pain in the back and stomach. Tonsillectomy was done in 1929 and a unilateral cryptal infection was found. He was not seen again until 1937; roentgenograms taken at that time showed calcified nodes in the left hilar area. There was no clinical tuberculosis.

Case 27. A child, 5 years old, was admitted who was poorly developed and nourished. Her mother had died with pulmonary tuberculosis. Physical examination showed large nodes at the angles of the jaw but the lungs appeared clear. The child had a positive tuberculin reaction, and roentgenograms showed increased hilar density. Tonsillectomy was done on July 23, 1928. Microscopically a proliferative tuberculous lesion was present in one tonsil but a definite relation to either crypts or follicles could not be established.

Case 29. A girl, 6 years old, was brought in because of a limp in the right leg of 2 weeks' duration. There was restricted rotation and adductor spasm. The tonsils and cervical lymph nodes were enlarged. She was treated for tuberculosis of the hip. On April 11, 1939, tonsillectomy showed a unilateral cryptal tuberculous infection. Several roentgenograms showed hilar enlargement but no parenchymatous lesions of the lungs.

Case 30. A white boy, 3½ years old, was admitted who had been followed in the clinic since the age of 6 weeks. No exposure to tuberculosis was known. There had been frequent attacks of otitis media. On February 21, 1934, tonsillectomy was done. There was a unilateral cryptal infection. Roentgenograms on May 23, 1934, showed hilar accentuation; those on November 27, 1936, showed a similar appearance.

Case 31. A boy, 8 years old, was admitted whose mother had active pulmonary tuberculosis. She brought the boy into the hospital because she thought that he had chickenpox. The lesions were insect bites, however. Tonsillectomy was done on December 9, 1929. There was a unilateral cryptal infection. Roentgenograms on February 10, 1930, showed calcified nodes in the right hilus; those on January 13, 1941, showed a similar picture.

Case 33. Tonsillectomy was done on a white male, 22 years old, on March 29, 1924. Microscopically one of the tonsils showed a proliferative tuberculous lesion, but it could not be related definitely to crypts or follicles due to the way the section was cut. Patient was called in for a recheck. The chest was found to be negative. Roentgenograms were advised but the patient refused.

Case 34. A patient, 31 years old, came in with complaints of stomach ulcer. There was no family history or past history of tuberculosis. The lungs were negative; tonsils were slightly enlarged, and cervical lymph nodes were palpable. Tonsillectomy was done on January 31, 1930. Microscopically there was a unilateral cryptal infection. No further studies were carried out.

Discussion

Cases 1, 5, 6, 7, 8, 11, 12, 14, 18, 23, 24, 29, 30 and 31 are most easily interpreted as primary tuberculosis of the tonsils. In some instances the available data suggest the possibility of bovine organisms as the infecting agents. Case 25 is less clear owing to the age of the patient. Data on cases 27, 33 and 34 are incomplete.

Unilateral Infections with Pulmonary Tuberculosis

Case 13. A white woman, 58 years old, was admitted complaining of bone and joint pain. Many years ago she had had an attack of pleurisy. Tonsillectomy was done on May 10, 1927. There was extensive scarring of both tonsils with unilateral cryptal tuberculosis. Patient was called in for a recheck and on June 14, 1927, roentgenograms showed thickening and infiltration of the right apex, probably tuberculous.

Case 15. A white woman, 36 years old, was admitted complaining of chronic backache. Tonsillectomy was done on December 1, 1927. There was a unilateral cryptal infection. Roentgenograms of the lungs on December 16, 1927, showed calcified hilar nodes and probable cavity at the right apex. There were râles in the right apex posteriorly. Treatment was undertaken at home. Roentgenograms on May 7, 1937, showed inactive parenchymal lesions in the right apex.

Case 17. A white man, 25 years old, was first seen on April 29, 1924, with the complaint of hoarseness of 2 months' duration. This had followed an attack of tonsillitis or sore throat. Physical examination was essentially negative except for slight enlargement of the cervical lymph nodes. Pus could be expressed from the upper pole of the right tonsil. Tonsillectomy was done on May 5, 1924. Microscopically there was a unilateral infection consisting of one tubercle with a necrotic, partially caseous center. The specimen was too distorted to determine whether it was related to the crypts. The tonsils were extensively scarred. Re-examination of the chest showed signs of active tuberculosis, and roentgenograms on May 23, 1924,

showed an extensive bilateral parenchymatous infiltration, with a large cavity on the left side. The patient was not seen again.

Case 19. A white man, 29 years old, came in complaining of sore throat and frequent attacks of tonsillitis. There was no history of tuberculosis in the family. Physical examination showed a partial stricture of the nasopharynx but no positive findings in the lungs. Tonsillectomy and plastic operation were done on January 3, 1924. Microscopical examination showed a diffuse epithelioid reaction with giant cells in one tonsil, without caseation or necrosis. The section did not include any crypts. A relation to germinal follicles could not be made out. The tissue from the nasopharynx showed extensive productive tuberculosis. Roentgenograms in 1926 showed evidence of apical pleuritis with thickened pleura at the right base.

Case 20. A white boy, 8 years old, was admitted with no history of exposure to tuberculosis. Tonsillectomy was done on April 20, 1927, following which he did not do well. There was a unilateral cryptal infection. On May 3, 1927, a few fine râles were heard in the left interscapular region. Roentgenograms on May 5, 1927, showed an area of consolidation in the midportion of the left lung with hilar enlargement and infiltration of both upper lobes.

Case 21. A white girl, 5 years old, had been followed since early infancy. A roentgenogram taken on August 30, 1930, showed a small but definite amount of fibrosis in the right upper lobe. Tonsillectomy was done on September 9, 1930. Both tonsils were removed but only one reached the laboratory. This showed a localized cryptal infection. Roentgenograms on September 28, 1931, showed some accentuation of the hilar areas and an area of increased density in the right upper lobe which appeared to be tuberculous.

Case 26. A white man, 37 years old, was referred to the hospital for tonsillectomy. Operation was done on March 25, 1937. There was a unilateral cryptal infection. Roentgenograms on November 9, 1937, showed multiple lesions in both upper lobes. The sputum was positive for tubercle bacilli and there was an early laryngeal tuberculosis.

Case 28. A white female, 24 years old, was given a routine physical examination on February 10, 1931, which disclosed no abnormalities. Tonsillectomy was done on December 22, 1933, and unilateral cryptal tuberculosis was found. She was called in for a recheck and gave a history of fatigue and lose of weight. Roentgenograms on January 26, 1934, showed bilateral parenchymatous lesions with a probable cavity on the left side.

Case 35. A white man, 20 years old, was a known case of pulmonary tuberculosis. Tonsillectomy on November 3, 1923, showed a unilateral infection, but due to the poorness of the section the morphological type could not be diagnosed. This patient was known to have sputum positive for tubercle bacilli.

Discussion

Four of these cases were active and probably open, so the sputogenic origin of the tonsillar lesion seems fairly certain. Case 13 was apparently neither active nor open. Assuming this to be true, it must have been a post-primary exogenous infection. This should not seem strange, in view of the ubiquity of the organism and the frequency of tonsillar erosions. From the scarred appearance of the tonsils in this case it might be guessed that there had been previous infections, some of which could have been sputogenic. Data on cases 17, 19, 21 and 35 are incomplete.

Bilateral Cryptal Infections

Case 3. A colored child, 14 months old, was nursed for a short time by his mother who died of pulmonary tuberculosis 3 months after his birth. There were enlarged cervical, inguinal and axillary lymph nodes. Tonsils were enlarged. Roentgenograms on June 30, 1931, showed enlarged hilar nodes. Tonsillectomy on September 30, 1931, showed a bilateral cryptal tuberculosis.

Case 9. A white woman, 24 years old, complained of an ache in the upper chest and shoulders following an attack of tonsillitis. Physical examination was essentially negative except for chronic tonsillitis and enlarged cervical nodes. Tonsillectomy was done on August 15, 1924. Microscopically there was a widespread bilateral infection arising in the crypts. The patient was called back for a recheck but no evidence of extratonsillar tuberculosis was found. However, roentgenograms were not made.

Case 10. A white man, 30 years old, complained of a "run-down" feeling, and pain below the shoulder blade on the right side. There was impairment to percussion in the same region. Roentgenograms showed an extensive, radiographically inactive, infiltration of both upper lobes. Tonsillectomy was done on October 1, 1925. There was a bilateral cryptal infection.

Case 16. A white male, 29 years old, complained of chills, fever and night sweats over a period of 6 months. There were moist râles in the left interscapular region. Roentgenograms on February 16, 1929, showed active parenchymatous changes in the right upper and middle lobes. Tonsillectomy was done on March 4, 1929. There was a heavy infection arising in the crypts of both tonsils. The patient died elsewhere a few months later.

Case 22. A boy, 12 years old, was brought in for a routine tonsillectomy. There was no family or personal history of tuberculosis. Physical examination was negative except for large and injected tonsils and palpable cervical nodes. Tonsillectomy was done on March 19, 1928. There was a bilateral cryptal infection with much scarring. The patient did not return for a recheck.

Case 32. A white woman, 22 years old, had been followed because of a gynecological complaint for about 1 year when an examination of the chest showed an enlargement of the retrosternal dullness. On March 20, 1925, roentgenograms showed a large rounded nodule in the right hilus. The impression was lymphosarcoma. She was given x-ray therapy and roentgenograms on May 29, 1925, showed that the circular shadow had almost disappeared. On November 16, 1925, she had a severe attack of tonsillitis. About 3 months later a huge cervical lymph node had developed. There was no general glandular enlargement. Specimen taken for biopsy of this node showed tuberculosis. Tonsillectomy on May 20, 1926, showed a massive bilateral infection clearly arising in the tonsillar crypts. Following the excision for biopsy a draining sinus developed which persisted for many years.

Discussion

Case 9 appears to be the result of a heavy infection by the oral route, which could have come from infected milk or some similar source. Case 32 also seems to be an oral infection, interesting because of the severe degree of lymphadenopathy, and similar in many respects to case 3. Because of lack of evidence, case 22 cannot be commented upon. Some or all of these four cases may have been due to a bovine type of infecting organism. Mitchell [6, 7] isolated the bovine organism 65 times and the human organism 7 times in a series of tuberculous

cervical nodes. In 26 cases of tuberculous tonsils he found the bovine type 20 times. Case 16 is clearly, and case 10 probably, of sputogenic origin. Long, Seibert and Gonzalez,[5] in the study of 81 cases of tonsillar tuberculosis, secured roentgenograms on 35 patients and found active pulmonary tuberculosis in 18 (16 of the adult type, 2 of the childhood type). The infection in these tonsils appeared to originate in the crypts. However, Long and his associates had a small series of "closed" cases where the histological picture was similar to that seen in the "open" cases. The mechanism of infection was uncertain. Possibly they may have been post-primary infections with no relation to the pulmonary lesions.

Bilateral Follicular Infections

Case 2. A white male, 33 years old, was first seen on December 24, 1932, 1 month after an attack of sudden weakness, chilliness and sweating. Following this he continued to feel weak and tired, ran an irregular fever and lost 11 lbs. Physical examination was essentially negative. The tonsils were small. Innumerable laboratory studies were done without finding the source of the trouble. Tonsillectomy was done on January 11, 1933. He left the hospital and, in another city, shortly developed a severe sloughing infection of the tonsillar beds, necessitating hospitalization for several days. The patient was not seen again at the hospital, but in 1939 he wrote asking that his clinical history be forwarded to the physician who was treating him for a "recurrence of his trouble." The tonsils in this case showed many small tubercles located near, and in some cases in, the germinal follicles. There was no apparent relation to the crypts.

Case 4. A white boy, 4 years old, was first seen on June 22, 1931, with complaint of loss of appetite and persistent pain on the left side of the chest. An uncle, who had lived with the family in constant contact with the patient, had died recently of advanced pulmonary tuberculosis. On admission to the Henry Ford Hospital the tonsils and cervical nodes were moderately enlarged. A few fine râles were heard over both upper lobes. Roentgenograms on June 30, 1931, showed accentuated hilar areas, enlarged nodes in the left hilus and suggestive evidence of a cavity at the left base; those on August 4, 1931, showed evidence of consolidation at the left base. Tonsillectomy was done on March 16, 1932. There was a bilateral infection with hard tubercles located near and in the germinal centers. In some areas there was a nonspecific follicular necrosis. Roentgenograms on July 8, 1932, showed no definite parenchymatous changes although there was suspicious infiltration of the hilar areas.

Discussion

The history in case 2 is quite compatible with the histopathological finding of a follicular infection. In case 4 conditions favorable for a sputogenic infection may have been present, yet blood stream infection took place instead. Under similar conditions a mixed cryptal and follicular infection might occur.

General Discussion and Summary

Relation of Tonsillar Tuberculosis to Tuberculosis of Cervical Nodes. Blatt and Greengard[8] stated that whereas some authorities believe tuberculosis of the cervical nodes to be almost invariably due

to bovine organisms with the tonsil as the portal of entry, they, on the contrary, lean to the belief that it occurs most commonly as a result of primary aerogenous infection of the lungs with secondary involvement of the intrathoracic nodes, followed by direct extension to the deep and superficial cervical nodes. Unless I carry the process one step further and assume that the tonsils are infected through the cervical nodes, it would be difficult to explain my cases. Such a retrograde lymphatic infection of the tonsil seems unlikely. Case 8 clearly suggests a sequence of infection from the tonsil to the cervical nodes, as do cases 11 and 5.

Tonsillar Tuberculosis and Hilar Tuberculosis. On the other hand it is possible that the mechanism suggested by Blatt and Greengard [8] takes place in reverse, so that the infection may travel from the tonsils to the cervical nodes, thence to the hilar and even to the retroperitoneal nodes. Cases 3, 12, 18, 24, 31 and 32 are in point here.

Tonsillar Tuberculosis and "Open" Pulmonary Tuberculosis. It would appear highly probable that most tonsillar infections in this group are sputogenic. A few cases of hematogenic infection will occur also. When the pulmonary lesion is "closed" and the pathological picture in the tonsil is that of a cryptal infection, the dilemma is resolved by postulating a post-primary exogenous infection of the tonsil independent of the lesion in the lung, or a reawakening of a slumbering infection incurred at a time when the pulmonary lesion was temporarily "open."

Hematogenic Tuberculosis of the Tonsils. Weller [1] found 16 of 204 cases to be of this type. In this series there are 2 out of 35 (or 28, if the doubtful cases are omitted). Apparently cases of hematogenic infection are considerably in the minority.

Primary, Post-primary and Hematogenic Infections. In this series, 18 cases (1, 3, 5, 6, 7, 8, 9, 11, 12, 14, 18, 23, 24, 25, 29, 30, 31, 32) have been interpreted as primary; 7 cases (10, 13, 15, 16, 20, 26, 28) as post-primary sputogenic; 2 cases (2, 4) as follicular. The remainder are more or less uncertain for various reasons.

Pathogenesis of Tonsillar Tuberculosis. Cryptal infections are due to the passage of the bacillus through the intact or eroded mucosa of the base of the crypt. Tubercles related to the follicles and germinal centers are hematogenous. Lymphatic spread can be ignored because the tonsil has no afferent lymphatics and retrograde lymphatic spread is unlikely.

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